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Editor in Chief
Dr. Sunil Ganekal, MS, DNB, FRCS

From Editor's Desk

Dear Readers

This issue of the journal of vsion sciences (JVS) is dedicated to my mentor and legend in ophthalmology Dr SS Badrinath. This issue has an article on his journey and his vison in building temple of the eye (Sanakara Nethralaya).Other highlights include, editorial on ophthalmic research, How to select a right scientific Journal for publishing the research paper. This issue also includes number of review articles written by many eminent ophthalmologists covering various ophthalmic subspecialities, interesting case reports, surgical pearls and postgraduate corner. Life beyond ophthalmology section covers fininacial tips, investment options for the Doctors and art of charcoal painting.Do feel free to write to me regarding any suggestions and feedback at editorjvsjournal@gmail.com

- Dr Sunil Ganekal

Editor-in-chief JVS

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How to select a right scientific Journal for publishing the research paper

- Dr. Sunil Ganekal
Davangere Netralaya, Karnataka

Introduction

Digital technologies and new publishing models such as Open Access coupled with the democratization of publishing worldwide has transformed the traditional print journal model for communication and dissemination of knowledge. In spite of the vast array of publishing opportunities in today's digital world that allow authors to reach a wider audience, authors face an unprecedented challenge when selecting a journal to publish their research. There are now over 80,000 academic, peer-reviewed English language journals currently active as of July 2019 and 30,000 of these journals are classified under Medicine and Health.[1]

In light of the proliferation of journals, some journals have come under increased scrutiny recently with terms such as questionable, predatory, pseudo, deceptive, unscrupulous, illegitimate, or dishonest, used to describe these journals.[2,3] Per Cobey,[4] et al., there is no standardized definition of questionable journals but the International Committee of Medical Journal Editors (ICMJE) offers a description: "These journals (predatory or pseudo-journals) accept and publish almost all submissions and charge article processing (or publication) fees, often informing authors about this after a paper's acceptance for publication. They often claim to perform peer review but do not and may purposefully use names similar to well established journals."[5] Additional characteristics of these journals described by Masten and Ashcraft include offering no services such as "expert peer-review, editing, archiving, indexing, and promising almost instant publication."[6] Shamseer, et al., note 13 salient characteristics of potential predatory publishers such as no retraction policy, homepage language targeting authors, scope includes non-biomedical subjects alongside biomedical topics, manuscript submission via email, and others.[7]In December 2016, the International Committee of Medical Journal Editors (ICMJE) announced revised recommendations for authors: "A growing number of entities are advertising themselves as 'medical journals' yet do not function as such (predatory journals)." The advice to authors was: "Authors have a responsibility to evaluate the integrity, history, practices and reputation of the journals to which they submit manuscripts." The National Institutes of Health (NIH) issued a notice in November 2017 reporting an increase in journal articles generated with NIH-funded research published in journals or by publishers that do not follow best practices.[8] NIH issued several recommendations for authors to ensure the credibility of their research findings when publishing:

- **Adhere to the principles of research integrity and publication ethics;**
- **Identify journals that follow best practices promoted by professional scholarly publishing organizations; and**
- **Avoid publishing in journals that do not have a clearly stated and rigorous peer review process.**

How can authors evaluate the integrity, history, practices and reputation of journals? There is no reliable list of good vs. bad journals, nor is there an automated decision-aid tool to use for identifying journals that are suitable for publication. We recommend that authors begin their list of potential journals by considering the journals they use for their research or clinical care. Other potential journals include journals from publications that authors cite in their research, journals they review for, and journals associated with their professional organizations. Mentors and colleagues may also be able to provide insight as to which journals are regarded as relevant for an area of research or are recommended for tenure and promotion purposes. Consultations with mentors and colleagues can be especially important for early-career authors and authors tackling a research topic outside their primary field. Other criteria to consider are noted below.

Criteria for Evaluating a Journal

Scientific Rigor

A key indicator of journal quality is the scientific rigor of the publications published in the journal. When considering publishing in a new or unfamiliar journal begin with a review of publications published over the past few years to assess details such as the purpose of the research, design and methodology, data analysis, results, and discussion, all of which can lend insight as to scientific quality. Tables and figures should be clearly marked, legible and appropriate for the data. References should be comprehensive and current. The procedures used by the journal for ensuring scientific rigor during the peer review process also lend insight as to commitment to scientific rigor. Plagiarism checks using software such as iThenticate, using different statistical testing to confirm data validity, and applying forensic tools to detect image manipulation are examples of practices that reputable journals follow to ensure scientific rigor.

Another clue as to scientific rigor is whether the journal requires use of recognized guidelines for reporting of research. Reporting guidelines help to ensure the quality of scientific research and enhance the replicability of the research. Examples of reporting guidelines are CONSORT, PRISMA, and STROBE, to name a few. As of July 2019, there are over 400 reporting guidelines per Equator Network.[9] A similar requirement by journals is registration of clinical trials before the time of first patient enrollment to be considered for manuscript review. Transparency of journal practices and policies for data sharing is another factor to consider for assessing scientific rigor. Data sharing is integral for ensuring that science is transparent and reproducible, and promotes the integrity of research and fosters public trust. A recent Pew Report in 2019 found that a majority of U.S Adults (57%) trust scientific research findings more if the researchers make their data publicly available.[10]

Editorial Quality

Editorial quality noted in publications including editorials, can provide clues as to journal quality. Misspellings, grammar and punctuation errors, or lack of clarity and cohesiveness in writing is indicative of lack of editorial oversight and reviewer commitment. These clues may signal a journal that is not appropriate for publication. Titles and abstracts themselves can also be revealing as to editorial quality—a title that is not descriptive or an abstract that needs to be read more than once may be a warning sign.

Peer Review Process

Transparency as to the peer review process is a benchmark of journal quality. A reputable journal will fully disclose the peer review process including criteria used for peer review, selection of reviewers, the type of peer review, timeframes for the peer review, and how the peer review process is handled by the editorial board. Additional details such as how conflicts of interest are handled, confidentiality, and other ethical standards for peer reviewers should also be available from the journal website.

Ethics

A quality journal will include information as to issues such as plagiarism, conflicts of interest, internal review board approval, informed consent, human and animal subject research, confidentiality, fraud, salami (or segmented) publications, ghost authorship, data and image manipulation, and other ethical considerations. A journal should include information as to ethics on the journal website, what their expectations are of authors and how they address these issues. Reputable journals endorse guidelines and best practices for publishers such as the International Committee of Medical Journal Editors (ICMJE), Committee on Publication Ethics (COPE), and the World Association of Medical Editors (WAME).

Editorial Board Members

A review of the journal editorial board can reveal valuable insights as to the quality of a journal. Editorial board members should be known as established experts in the field related to the aim and scope of the journal, affiliated with known institutions, and hold appropriate academic credentials. Contact information for editorial staff should also be available. If information is missing from the journal website or if there is no contact information for editorial board members, additional review is recommended before submitting a manuscript for peer review.

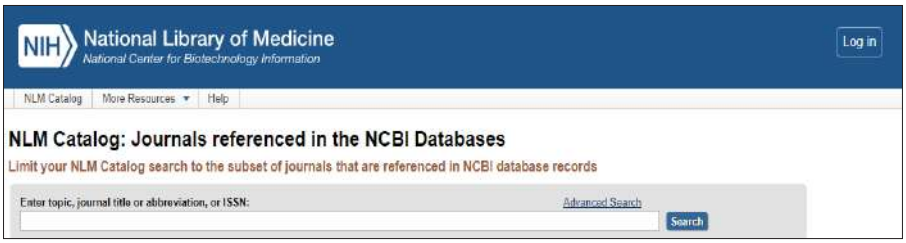
Another clue related to editorial quality is editorials authored by the Editor-in-Chief or members of the editorial board. Editorial board members from reputable journals will contribute frequent and thoughtful editorials that provide context or significance to publications for a specific issue or discuss updates in journal policies for authors and readers.

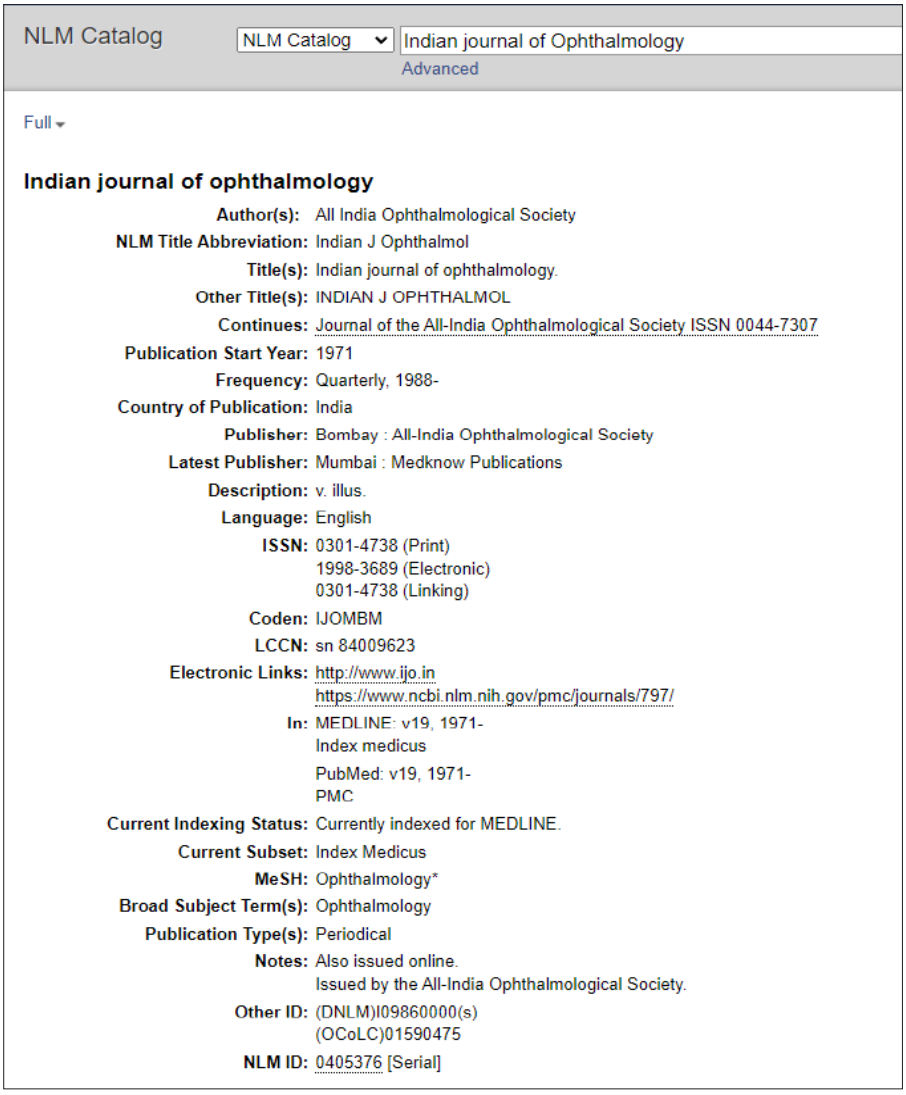
Journal Reputation/Business Model

The reputation of a journal includes the publisher of the journal, the societal organization that sponsors the journal, aim and scope, mission statement, among other criteria. The publisher of a journal or the sponsoring society can lend strong credence to the quality of a journal. The aim and scope should be clearly stated and other information such as a mission statement or sponsoring organizations helps to assess the reputation of the journal. The business model of a journal should be evident and if there are fees for publication, the fees should be clearly stated on the journal website—in other words, there should be no surprise fees after submission of a manuscript for peer review.

Author Rights and Copyright

The journal policy as to author rights and copyright is another benchmark of a quality journal. Copyright is a bundle of rights that allows authors to use, disseminate, display or modify the work in any medium. Up until 20 years ago, authors routinely transferred all rights to their work to the journal publisher upon publication. Many journals allow authors generous uses of the work after publication and in some instances, will allow authors to retain full rights to the work. Authors are advised to anticipate any future re-uses of their publications before selecting a journal and signing a copyright agreement form. Some authors are required to comply with public access mandates from organizations such as the National Institutes of Health (NIH) or the National Science Foundation (NSF). If a journal does not allow for compliance with public access mandates, authors will need to consider another journal. Some journals allow oral rights to the work or reuse of a figure or table in a subsequent work, or posting of the work on a repository; others do not. Journals may also stipulate various uses based on the version of the work (preprint, post-print, and final published version). Transparency of a journal's copyright policies for authors is indicative of a quality journal.





Indexing Status

Authors want their research to be discoverable and read by others. A quality journal will be indexed by major bibliographic and citation databases such as MEDLINE®, Elsevier Scopus and EMBASE, Clarivate Analytics Web of Science, Cumulative Index for Allied and Health Literature (CINAHL), and others. MEDLINE® is produced by the National Library of Medicine (NLM) and has rigorous scientific and editorial criteria for journals selected for indexing in MEDLINE®. Among librarians at our institution, Bernard Becker Medical Library, MEDLINE® indexed journals are considered to be the premier journals in the biomedicine field and many authors rely on MEDLINE indexing status as a strong indicator of a quality journal. In addition, MEDLINE® is a freely available citation database with no subscription required so any author can check for indexing status. As of July 2019, there are 4,995 journals currently indexed by MEDLINE® (Figure 1).

However, some journals claim to be indexed by PubMed® which can be confusing as MEDLINE® citations are found in PubMed® along with citations to full-text articles from PubMed Central® (PMC). PubMed®, MEDLINE®, and PMC® are separate entities with different purposes.

- PubMed® is a resource that aggregates citations from MEDLINE®, PMC®, and other resources from the NCBI Bookshelf.
- PMC® is a free archive of full-text journal articles.
- MEDLINE® is a journal citation database from the National Library of Medicine (NLM).

The single web interface of PubMed® blurs these

distinctions, leading to confusion for authors and in some cases, publishers. Journals that claim to be indexed in PubMed® or Google Scholar are cause for concern. When it comes to selecting a journal, we encourage authors to verify the indexing status of a journal using a bibliographic and citation database rather than relying on the journal website, or check with a librarian affiliated with your institution or a local public library.

Impact Factor Scores

Authors often use various journal impact factor scores as criteria for selecting a journal. The Journal Citation Reports Journal (JCR) Impact Factor score was developed in the early 1960s for selection of journals in the Web of Science citation database and as an acquisitions tool for libraries.[11] The JCR Impact Factor score evolved over the years to be associated with identifying "high impact" journals for publication.[12]

Other journal impact scores have been launched recently, including the Eigenfactor, introduced in 2008, and CiteScore, launched in 2016. Impact factor scores are calculated for indexed journals in the Web of Science and Scopus databases, and broadly, the calculations are based on the number of citations within a specific timeframe garnered by publications from journals. Some journals often note impact factor scores from sources such as a directory or a catalog which do not contain citation data. Authors should be wary of vague scores touted from non-citation data sources. A more holistic approach in selecting a journal is recommended instead of relying on impact factor scores. Per Ioannidis and Thombs, "Authors should pick target journals based on relevance and scientific rigor and quality, not spurious impact factors."[13]

Journal Operations

Journal operations include archival practices for articles using platforms such as PORTICO (https://www.portico.org/) or JSTOR (https://www.jstor.org/), whether a Digital Object Identifier (DOI) is assigned to articles or an International Standard Serial Number (ISSN) is assigned to the journal, and the publication schedule. An irregular publication schedule, excessive advertising, and missing or sporadic issues are indicative of unstable journal management. The aim and scope, editorial board, instructions for authors, and journal contact information should be available and easy to find.

Invitation to Publish a Manuscript or Submit an Abstract to a Conference

We are aware of many email solicitations for journal publication or invitations to submit an abstract for a conference, and in some cases, including invitations to speak at conferences. These emails are usually generic in nature and contain stilted or archaic language. Unrealistic promises are made such as acceptance of publication within hours and publication within days. Some emails include phrases such as "let us know how much you can afford towards the article processing charges." Table 1. Names, postal addresses and email addresses are taken from publication records found online in freely available databases and for some, the subject line of the emails match verbatim the title of a funded NIH award and the full Principal Investigator's name as noted in NIH RePORTER, (https://projectreporter.nih.gov/reporter.cfma), a freely available resource. There are instances where authors are invited to submit a publication in a journal such as those published by Annual Reviews and these invitations are usually sent by a known colleague in your field of research. If it sounds too good to be true, it usually is.

- Archaic salutation
- Hyperbolic language in email
- Poor grammar or misspellings
- Excessive use of exclamation marks
- Promises of swift review or immediate conference abstract acceptance
- Journal aim and scope and conference topic is not germane to your area of research
- The publisher or conference organizer is unfamiliar
- Journal or conference title is similar to an established journal or conference
- The publisher icon/logo is similar to an established journal
- No credentials for the editor, editorial staff, and/or editorial board members
- Indexing status for the journal is noted as PubMed® or Google Scholar or a directory
- Vague impact score for the journal or claims that the journal is high impact
- Inappropriate images or ads/animations on website
- Inconsistent publication or conference history/schedule
- No ISSN for the journal
- No DOI for the publications
- Request for fees upfront or waiver of all fees

Table 1-Email Solicitation Warning Signs

Emails from conferences or journals may be potential phishing attempts. If you are interested in a specific conference or journal but are unsure if it is genuine, apply commonly recommended techniques for handling suspicious email: don't click on any links in the email itself, rather type in the address for the conference or journal website on your browser. Then use the criteria described above to determine if the event or journal is credible.

Conclusion

Publishing in journals that are not reputable can diminish the credibility of your research, limit your career, and may result in little or no dissemination and uptake.

When selecting a journal for your publication, a good starting point are the journals that you, your colleagues, and mentors use for research and clinical care. The next step is to review publications in the journal you are considering to assess the scientific rigor and editorial quality of the publications. Transparency from the journal as to its aim and scope, the editorial board, indexing status, the peer review process, reputation, and policies for authors are among the key indicators of quality journals. These criteria can help identify quality journals suitable for publication. Two resources with additional guidance we recommend are: Think. Check. Submit. (https://thinkchecksubmit.org/) and Principles of Transparency and Best Practice in Scholarly Publishing from the Open Access Scholarly Publishers Association (https://oaspa.org/principles-of-transparency-and-best-practice-in-scholarly-publishing/). Another option for authors is to consult with librarians affiliated with your institution or a local public library. Librarians are well-suited to provide guidance in helping authors with selecting quality journals to consider for publication. While it involves some effort, performing due diligence in your evaluation of the integrity, history, practices, and reputation of a journal before submitting a manuscript will help ensure that your work gets the readership it deserves.

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The Cosmic Lord of the Temple of the Eye

Padma Bhushan Dr. Sengamedu Srinivasa Badrinath

is the legendary Chairman Emeritus of Sankara Nethralaya, a tertiary eye care institute and a not-for-profit eye hospital in peninsular South India.

Born on February 24, 1940, in Triplicane, Chennai (then, Madras), his desire to become an ophthalmologist was kindled because of a childhood impression of terminal blindness which made him relentlessly chase and praise qualitative ophthalmic care.

Graduating from Madras Medical College in 1964, he pursued graduate studies in ophthalmology in the United States of America at Grasslands Hospital, New York Post graduate medical school and Brooklyn Eye and Ear Infirmary till 1968. After working as a vitreo-retinal fellow (1968-1970) under the eminent guidance of Dr. Charles L Schepens from Massachusetts Eye and Ear Infirmary, Boston, he became a fellow of Royal college of surgeons (Canada) and the American Board of Ophthalmology by 1970.[1]

Returning to India in 1970, he devoted his time as a flourishing private practitioner in many private hospitals. In September 1978, Dr. Badrinath inspirationally founded Sankara Nethralaya, a unit of Medical Research Foundation, as ordained by His Holiness Sri Jayendra Saraswathi, venerable pontiff of the Kanchi mutt.

Let us read on the captivating story of how Dr. Badrinath or "Chief" as he is fondly called, went on to make Sankara Nethralaya what it is today…

Work was worship for Dr. SSB

Sankara Nethralaya, "The Temple of the Eye", was founded on the twin pillars of spirit of service and state-of-the-art science, where haves and have-nots beget equal eye care. The first foundation for any lofty endeavor is its infrastructure. At a time when elite equipment and technical know-how were not freely available in our part of the world, Dr Badrinath was very particular that modern machines and surgical theaters should form the mainstay of practice at Sankara Nethralaya. Though the institute has a frugal approach with a no-wastage policy, when it came to setting up cutting edge clinical practices, no stone was left unturned, even at a time when these were barely known in Indian ophthalmic circles.

Eye care for all was his tag line

However, Chief was very particular that none of these reflected on the cost burden for the patient. His mantra has always been accessible and affordable eye care of the highest quality to each and every person. The institute from its inception has adopted a charitable approach whereby the paying patients are charged fairly and never fleeced excessively. A sizable segment is treated free of cost and on absolute par with paying patients, based on their socio-economic status. The community wing at Sankara Nethralaya continues to be a beacon of hope for thousands of visually impaired patients who cannot afford modern eye care.

He nurtured a nested community with shared vision

In a developing country with restricted resources, how was this even possible?

Dr. Badrinath set about the task of gathering like-minded individuals including ophthalmic professionals as well as friends of the community. The senior consultants, most of whom continue to serve SN till today, ably supported him as they were aligned with him both in interest and attitude and gave and their heart and soul to the upbringing of the institute. They paved the way for the high clinical and surgical treatment standards which are continued to be followed by their fortunate followers till today. Free thinking in day-to-day clinical practice was always ensured and assured in Sankara Nethralaya within the confines of a disciplined approach. Chief never imposed a restriction on any consultant or surgeon regarding the approach of her or his patient care. Also, the environment here was made very conducive for unrestrained clinical academic activity with no undue pressure on consultants regarding quantitative performance beyond reasonable limits.

Philanthropic support found its way to Chief

The message soon spread of about Dr Badrinath's efforts both through word of mouth and his personal approach. Every good action has a self-propagating ripple effect and he managed to garner a large number of philanthropic contributions from individuals and institutes both from our country and abroad. These flowed in to create the financial base for forming the institute and continue to be a major economic resource till today.

He reveled in the charm of the past as well as the promise of the future

Sankara Nethralaya has always been a blend of tradition and modern and best of both worlds too. While age old concepts of discipline and empathy in patient care are emphasized, every new development which is worthwhile is given importance and expansion in our institute. Employing electronic medical records, bringing outreach suburban camps back to the hospital base, commissioning mobile surgical units to serve the rural population incorporating state-of-the-art surgical care and introducing teleconsultation as a platform for patients who cannot visit are examples of some activities deployed by Dr. Badrinath at SN, which were much ahead of their time. Many of these modern technologies were tested and tried at our institute even when they were in the fledgling stages in most other places.

His vision included remote outreach and patronage of sister concerns

Chief also believed that eye care may be made affordable and state of the art but may still benefit only the urban population. He insisted on a decentralized approach where people in suburban and rural areas would get the same kind of care. So, the institute itself has branched out in three or four suburban areas and the rural camps are also conducted with financial support from charitable trusts. In contrast to the popular practice of camps being conducted outdoors in remote areas which was prevalent in those times, Chief believed in bringing camp patients back to the base hospital. This ensured that people in remote corners got accessible treatment and yet the strictness of surgical care including the aseptic precautions and availability of proper equipment was uncompromised when the surgery happened in the base hospital. Afterwards, it is ensured that dedicated teams followed up the patient till the final recovery and glasses also given free of cost.

Yet another approach that Dr. Badrinath adopted to expand treatment facilities was to nurture up and coming institutes. While usual corporate mentality is to covet patient catchments, he believed that every patient should get good eye care whether from Sankara Nethralaya or elsewhere. He has liberally contributed both his advice as well as resources to other ophthalmic institutes which owe much of their success to his efforts.

Dr. Badrinath had firm faith that mentoring is an asset

Tough as it was to bring about these achievements, Dr Badrinath foresaw that they should be propagated in the future as well so to ensure that the good work does not stop with the present generation. So, Chief focused a lot on teaching and training activities in Sankara Nethralaya. Every consultant who joins Sankara Nethralaya also signs up for academic activity as this is a teaching institute. SN has taught and trained hundreds of postgraduate students and fellows in various ophthalmic sub-specialties. These trainee doctors get deep insight into the clinical and surgical patterns in our institute and when they branch out into their own professional life, they carry most of these practices. SN has always been host to top notch ophthalmic clinical and basic science faculty from around the world and their premium guest lectures.

These alumni have an excellent rapport with the parent institution for mutual patient care referral and management. They also serve as brand ambassadors who highlight and propagate the ideals of Sankara Nethralaya

to the outer ophthalmic world. A dedicated SN alumni meet is organized every year with great vigor to restore and renew the special relationship between the alumni and alma mater.

Chief's most valuable legacy is the SN family

A man of many facets, our Chief's kaleidoscopic interests include watching classical art forms and sepia tinted block busters, following cricket matches, generously entertaining guests and enjoying South Indian cuisine as well!

Those who have read the Harry Potter series may be familiar with the "Room of Requirement". The room of requirement is a magical place inside which a person gets rewarded with whatever they need at that point in time. If somebody is hungry then the room of requirement gives some food, if somebody goes to learn it turns into a library and if someone wants to travel then the room becomes a transport bay and so on. Sankara Nethralaya, like wise has been wisely designed by our Chief, to be a room of requirement for ophthalmic patients and professionals alike. While it is a haven for patients to get affordable eye care in a hassle-free manner, it has also satisfied the aspirations of generations ophthalmic professionals and paramedics. It has been a zone for research for the researcher, a state-of-the-art institute to practice surgery for the surgeon and an altar of academics also. Almost every single professional who comes over here ends up getting what they wanted. When some eventually have to leave after training here to go out and pursue their own career, they may go out of SN, but the SN spirit never gets out of them or their practice. To the rest of us, the 'sense of belonging' that Chief has always inculcated has made Sankara Nethralaya our home away from home!

- Dr. Radhika Natarajan

Department of Cornea & Refractive Surgery
Head of the Dept. of Teaching and Training,
Sankara Nethralaya, Chennai

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Inherited Retinal Dystrophies - Clinical profile & Management

- Dr. Poornachandra B., Dr. Isha Acharya, Dr. Sajjan Sangai, Dr. Sherina Thomas, Dr. Priya B.V., Dr. Naresh Kumar Yadav

Department of Vitreo retina,
Narayana Nethralaya, Bengaluru, Karnataka

Introduction

Inherited retinal dystrophies (IRDs) are a large group of eye disorders which develop due to mutations in one or more genes that can result in irreversible visual loss and, eventual retinal photoreceptor cell death. They have a wide spectrum of presentation, with variations in severity and progression across the different IRDs. Some have onset at birth or early childhood while others show symptoms in adolescence and later.[1] Diseases like Achromatopsia, Retinitis Pigmentosa Sine Pigmento, and Oguchi disease may not have obvious changes on clinical examination and hence can be easily missed.

General differences between dystrophies and degenerations are as follows:[1]

Dystrophies	Degenerations
Inherited	Sporadic, Age related
Early onset, Non-inflammatory condition	Late onset
Bilateral	Unilateral or Bilateral
Usually, Symmetrical	Asymmetrical if bilateral

Retinal dystrophies can be classified based on-

- The retinal location involved: maculopathy - when central retina is involved.
- The type of cells affected - rods, cones, or both, retinal pigment epithelium (RPE), inner retina.[2]
- Progession: Stationary or progressive.

Genetics:

- It can be inherited in various modes as described below –
- ***Autosomal Dominant (AD)*** - In autosomal dominant inheritance, only one copy of a disease allele is necessary for an individual to be susceptible to express the phenotype.
- ***Autosomal Recessive (AR)*** - In autosomal recessive inheritance, two copies of a disease allele are required for an individual to be susceptible to express the phenotype.
- ***X-Linked Dominant (XD)*** - As in autosomal dominant inheritance, only one copy of a disease allele on the X chromosome is required for an individual to be susceptible to an X-linked dominant disease.
- ***X-Linked Recessive (XR)***- As in autosomal recessive inheritance, two copies of a disease allele on the X chromosome are required for an individual with two X chromosomes (a female) to be affected with an X-linked recessive disease.

We will be describing some of the commonly occurring IRDs for the scope of this article.

I Macular dystrophies:

Macular dystrophies can be further classified as follows:

Autosomal dominant	Autosomal recessive
Best macular dystrophy Pattern dystrophy Cone dystrophy	Stargardt disease
Sorsby fundus macular dystrophy	Glomerulonephritis type 2
Autosomal dominant radial drusen	Autosomal Recessive Bestrophinopathy
North Carolina macular dystrophy	
Dominant cystoid macular edema	

A. BEST Macular Dystrophy (BMD):

It is an autosomal dominant condition caused by the mutation in the BEST1 gene (VMD2) on 11q13 chromosome. It is one of the most common mendelian macular dystrophies occurring in about 1 in 10, 000 individuals. The characteristic macular lesion of the disease is its *egg-yolk*-like appearance centered on fovea **(Fig 1A)**. There is a 20% chance to develop choroidal neovascular membrane (CNVM) in one eye. (3)

The stages of Best macular dystrophy are as follows:

1. **Pre-Vitelliform stage–** There are subtle retinal pigment epithelium (RPE) changes with Electro oculogram (EOG) being abnormal.
2. **Vitelliform stage** – There is presence of round, elevated yellow macular lesion described as classic *'egg yolk'* appearance due to the accumulation of lipofuscin in the subretinal space and RPE.
3. **Pseudohypopyon stage–** Seen at puberty, when the yellow material breaks through RPE and accumulates in the subretinal space with a fluid level formation.
4. **Vitelliruptive stage**- Lesion breaks up with pigment clumping and early atrophic changes giving a *-'scrambled egg appearance'.*
5. **Atrophy stage**- It is a stage in which RPE atrophy occurs.

Sequelae**:** CNVM may develop with subretinal fibrous scarring.

Clinical features: Visual acuity is 20/20 or better in eyes with undisturbed vitelliform lesions till first six decades of life. Visual loss occurs when its complicated by nodular fibrosis, choroidal neovascularization or central geographic atrophy. Hyperopia with narrow angles may be present. Histopathologic findings: Increased RPE lipofuscin, loss of photoreceptors (often seen over a relatively intact RPE layer) and presence of sub-RPE drusenoid material and accumulation of cells and material in the subretinal space.

Optical Coherence Tomography (OCT) usually shows homogeneous hyper reflective lesion located between the outer nuclear layer and the RPE layer with areas of disruption of Ellipsoid Zone (EZ) while other layers remain intact **(Fig 1B)**. Outer segment elongation also may be seen. Fundus Autofluorescence (FAF) shows hyperautofluorescence at vitelliform stage and hypoautofluorescence later due to the atrophic RPE. The subretinal material is strongly autofluorescent (**Fig 1C)**. Electroretinogram (ERG) usually will be normal, **(Fig 1D)** whereas EOG is severely subnormal during all stages, **(Fig 1(E)** with Arden's ratio (The ratio of 'Light peak' to the 'Dark trough') being less than 1.5.

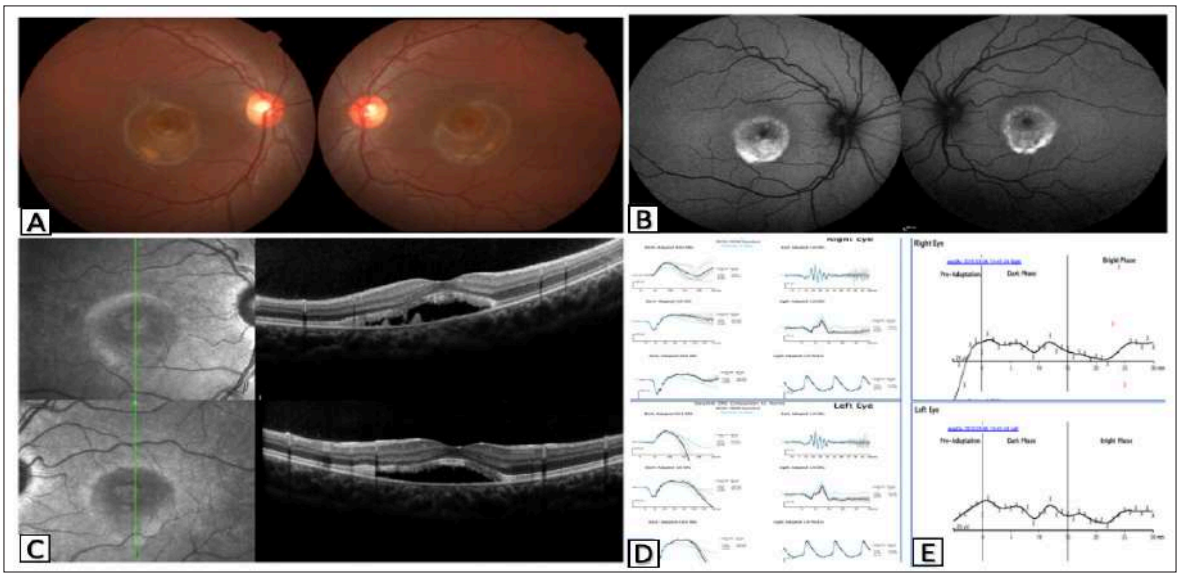

Fig 1. (A) - Fundus photo showing circular, elevated yellowish white macular lesion described as classic *'egg yolk'* appearance centred at the fovea. (B) SD-OCT showing homogeneous hyper reflective lesion located between the outer retina and the RPE layer with outer segment elongation while other layers being intact. (C) Auto Fluorescence Imaging showing hyperautofluroscent vitelliform deposits. (D) Normal ERG. (E) Severely subnormal EOG with absent light peak in bright phase.

Autosomal Recessive Bestrophinopathy (ARB):

It is a variant of Best disease which shows a compound heterozygous BEST*1* gene mutation exhibiting shallow subretinal fluid along with intra retinal fluid that can extend throughout the macula and beyond the arcades. Vitelliform lesions can occur as either solitary or multifocal form. **(Fig 2A)**

Clinical features: Visual acuity is worse than in autosomal dominant Best disease and Hyperopia is common. Sub-retinal lipofuscin deposits, predominantly outside the macula with accumulation of fluid within and/or beneath the neurosensory retina is seen.

Optical Coherence Tomography shows both intra retinal and subretinal fluid (**Fig 2B**). On Fluorescien angiography (FA) and FAF, the vitelliform subretinal deposits stain prominently and are hyperautofluorescent (**Fig 2** C-D). As opposed to BMD, ARB will have full field ERG abnormalities with reduced scotopic and photopic responses (**Fig 2E**). **EOG** will be abnormal with absence of light rise (**Fig 2**F)

Management for BMD and ARB primarily consists of recognizing choroidal neovascularization and hastening its regression with anti-VEGF therapy. Few patients may require peripheral iridotomy due to association with narrow angles and/or angle closure glaucoma. Patient should be cautioned against playing contact sports without protective gear. Protective eyewear is recommended for all sports. Patients require life time follow up to screen for glaucoma and CNVM development.

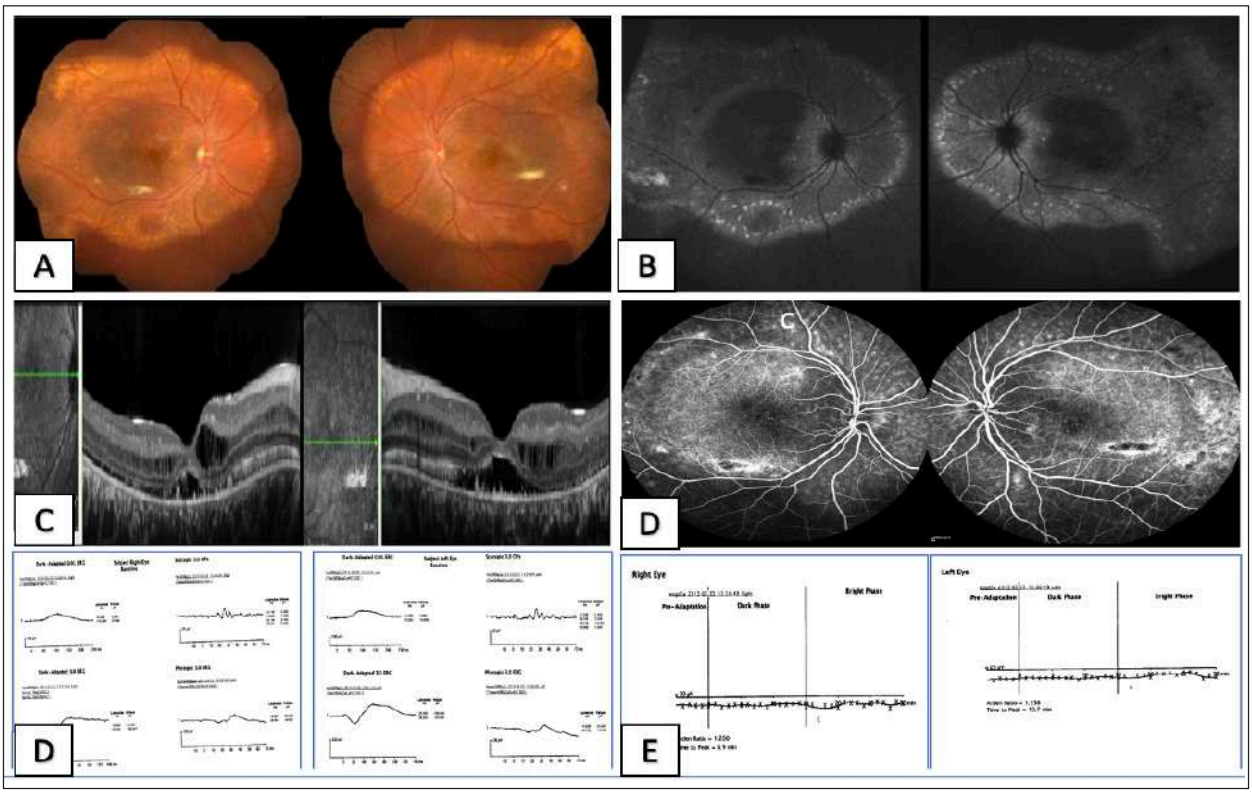

Fig 2 (A)Fundus photograph showing numerous yellowish white deposits scattered throughout the posterior pole and a patch of subretinal fibrosis just inferior to the fovea. (B) Spectral domain optical coherence tomography showing both intra retinal and subretinal fluid. (C) Fundus autofluorecence image shows the hyperautofluorescent vitelliform subretinal deposits. (D) Flurorescein angiogram of both eyes showing hyperfluorescent stained sub retinal deposits of lipofuscin. (E) ERG showing full field abnormalities with reduced scotopic and photopic responses in both the eyes. (F) - abnormal EOG showing absence of light rise.

B. Stargardt Disease:

It is the most commonly inherited macular dystrophy due to variations in *ABCA4* gene and is autosomal recessive. Mutation in *ABCA4* gene causes Stargardt's disease in 95% cases, Cone-rod dystrophy in 30-50% cases**,** AR Retinitis Pigmentosa in 8% cases.[4] 5% of patients with Stargardt show mutation in *ELOVL4, PRPH2,* and *BEST1* genes. ABCA4 gene is located on chromosome 1 and codes for the transport protein located on rim of rod and cones photoreceptors outer segments. Its function is to regenerate rhodopsin by accelerating removal of all trans – retinaldehyde from outer segments disc. It is characterized by accumulation of lipofuscin (specifically A2E (bisretinoid) which is the major component of lipofuscin) in the RPE cells, and also on the inner leaflet of the photoreceptor outer-segment disc membranes.

Clinical features:

The mean age of presentation may vary from 5 years or as late as 50 years. Visual acuity loss can range from mild to severe (20/30-20/200).The most characteristic fundus findings in Stargardt disease are light-colored flecks at the level of the retinal pigment epithelium. Fovea is generally normal or shows nonspecific mottling**.** Later stages may show oval area of foveal atrophy with '*beaten bronze*' **(Fig 3(A)** appearance with varying degree of yellow white flecks. It can have a Bull's eye configuration.

Optical Coherence Tomography usually shows foveal thinning with outer retinal loss, extent of which can vary according to the severity of the disease **(Fig 3(B)**. The scotopic and photopic ERG is normal in early stages, advanced cases may show reduction in amplitude of the waves. EOG tends to be subnormal. FA usually shows transmission hyperfluorescence due to window defects caused by RPE atrophy/ flecks. Characteristic blockage of choroidal fluorescence - dark choroid or silent choroid can also be seen.

Management:

Currently there is no proven treatment for the disease. Low vision aids, dark glasses can be advised. Patients need to avoid bright light and VIT-A /AREDS formulations so as to reduce bisretinoid formation. Future prospects of gene replacement therapy shows promising results from the ongoing clinical trials.

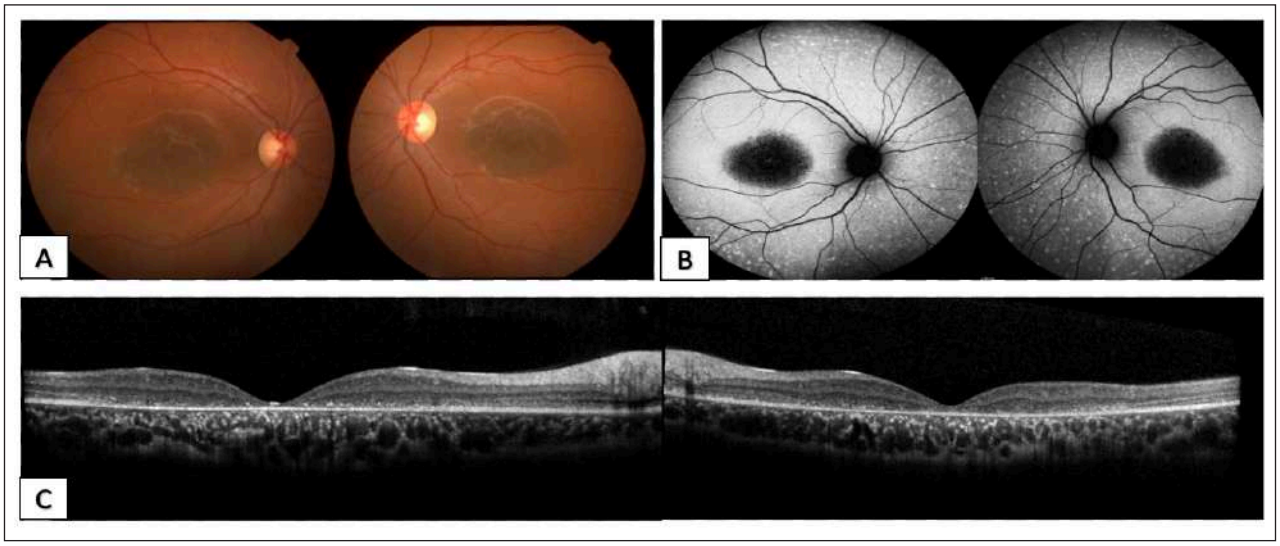

Fig 3. (A) Fundus photograph showing atrophic macular changes. (B) Autofluorescence imaging showing loss of autofluorescence in the atrophic fovea, flecks getting better highlighted. (C) Spectral domain optical coherence tomography showing selective loss of foveal photoreceptors and some part of the outer retina.

C. Fundus Flavimaculatus

It is included in the spectrum of Stargardt disease.

Clinical features: It is a disease of adult onset, which shows bilaterally ill defined, yellow white flecks extending to the mid periphery (**Fig 4(A-B**). It has a better prognosis as compared to Stargardt disease.

Investigations: ERG is normal in most cases and reduced Arden's ration is noted on EOG. FFA shows dark choroid due to lipofuscin deposits in RPE and window defects due to RPE atrophy.

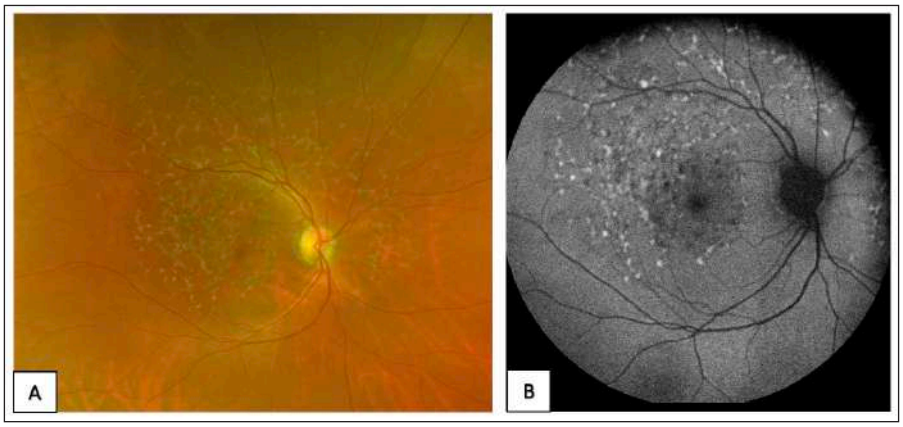

Fig 4 (A) Fundus photograph of the right eye showing extensive flecks throughout the posterior pole (B) Fundus autofluorecence (FAF) imaging of right eye showing hyperautofluorescent lesions at the posterior pole corresponding to the flecks on fundus photograph with fovea being spared.

D. Cone Dystrophy

These are a group of disorders which involves predominantly the cones. It can be classified as follows-

Early onset, Stationary	Later onset, Progressive
Complete and incomplete achromatopsia	Cone dystrophy
Blue cone monochromatism	Cone-rod dystrophy

Achromatopsia:

It is a rare autosomal recessive dystrophy with an incidence of 1 in 30,000.[5] Its characterized by poor vision since birth, poor colour vision, photosensitivity and may be associated pendular nystagmus.

Clinically, fundus may be normal or show subtle granularity or atrophy of macula. **(Fig 5A) Fundus Autofluorescence will show central hypoautofluroscence due to photoreceptor loss. (Fig 5B)**

On OCT usually there is disruption of ellipsoid zone in subfoveolar region, hypo reflective optically empty cavity may be seen **(Fig 5C).** Electroretinogram will have classic normal scotopic response with unrecordable or extinguished photopic responses.**(Fig5D)**

Management is with low vision aids, orange and red tinted glasses to reduce photophobia.

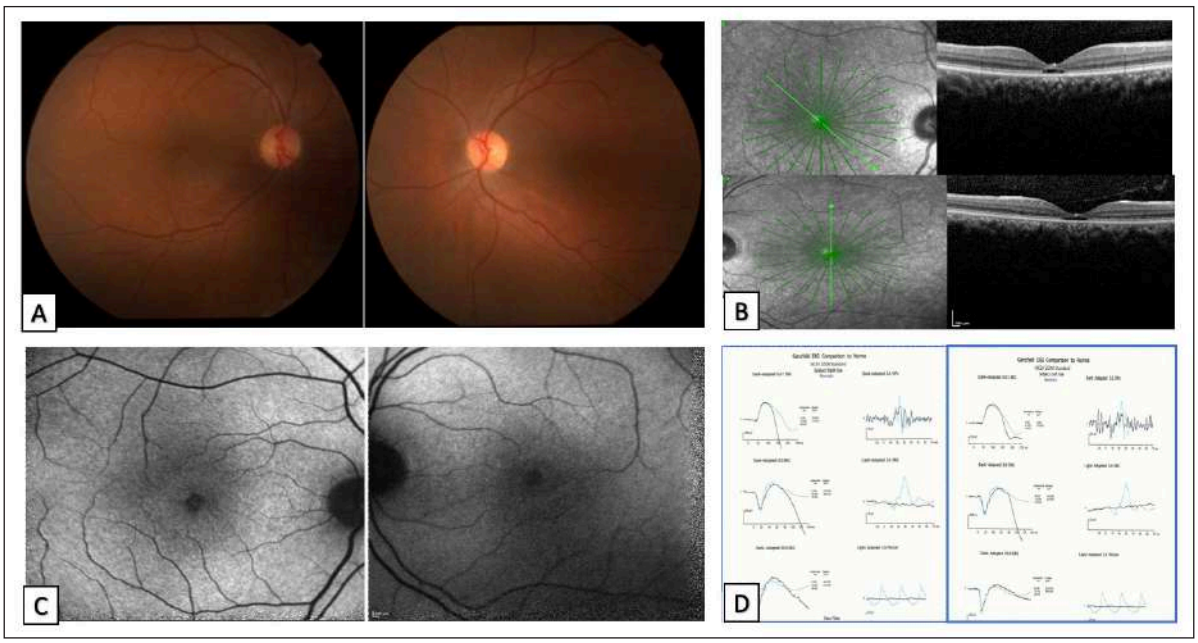

Fig 5. (A) Near normal fundus photographs in a patient of achromatopsia (Rod Monochromacy). (B) Autofluorescence imaging showing hypoautofluroscence due to photoreceptor loss. (C) Spectral domain optical coherence tomography showing disruption of ellipsoid zone seen as hypo reflective optically empty cavity and foveal hypoplasia. (D) Electroretinogram showing normal scotopic response with absent photopic response.

E. Progressive Cone Dystrophy

It is an AD inherited retinal dystrophy characterized by bilateral progressive loss of vision, photosensitivity and central scotoma. Clinically may have normal appearing fundus except with few atrophic changes and Bull's eye maculopathy in some cases **(Fig 6A)**.

ERG shows decreased photopic response and 30 HZ flicker with delay in implicit time (**Fig 6B**). Scotopic component can also get involved at later stages. **Multifocal ERG** shows reduced responses. On **OCT**, there is loss of outer retinal layers. (**Fig 6C)**

Management is with low vision aids and lenses that reduce photosensitivity.

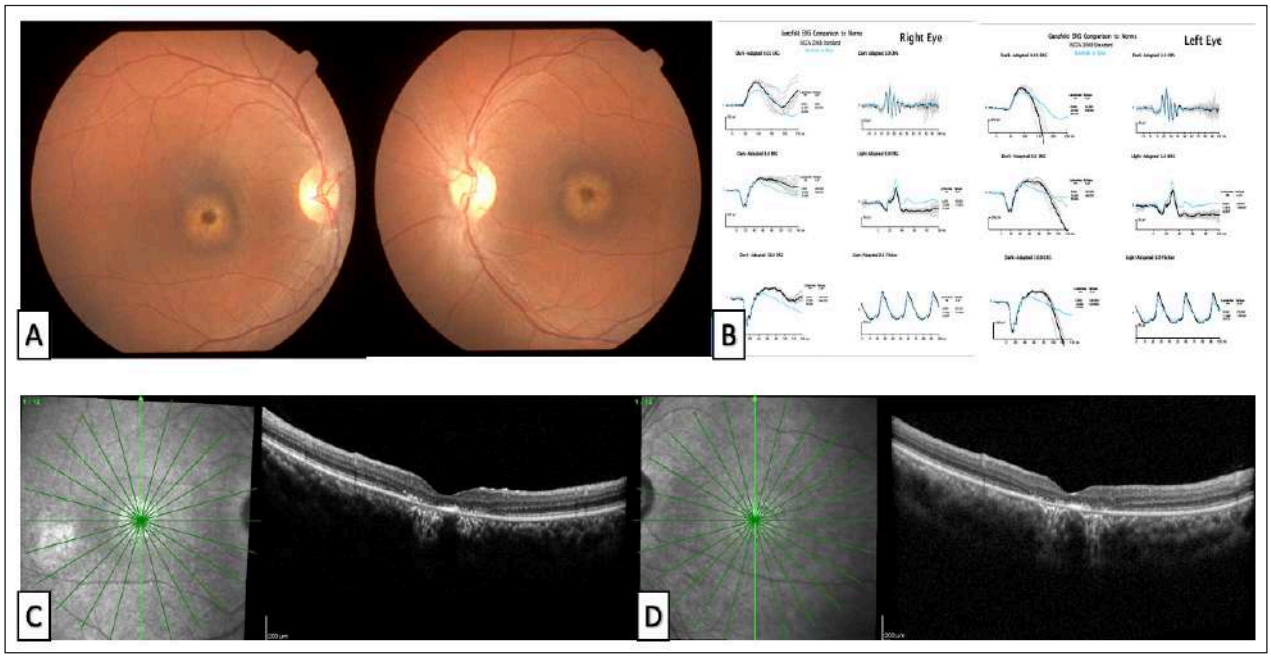

Fig 6. (A) Fundus photo showing Bull's eye maculopathy with some atrophic changes. (B) Electroretinogram showing decreased photopic response and 30 HZ flicker with delay in implicit time. (C) Spectral domain optical coherence tomography showing thinning of outer retinal layers with loss of photoreceptors at fovea.

F. X-Linked Retinoschisis

It is also one of the most common juvenile onset retinal degeneration in males with prevalence between 1 in 15000 and 1 in 30000.[6,7] In contrast to senile retinoschisis, the nerve split occurs in the nerve fiber layer, however schitic change may be seen in other layers also. Vitreous cavity may have floating unsupported blood vessels classically described as "Vitreous Veils".

It presents in the first or second decade with decrease in vision. Visual acuity ranges from 20/20 to 20/200. There is defective colour vision, field defects viz. absolute scotoma corresponding to location of peripheral retinoschisis.

Clinically most common manifestation is foveoschisis which shows *spoke wheel* pattern of folds radiating from the fovea in 70% **(Fig 7A)**. Typically, the peripheral retinoschisis is seen in inferotemporal quadrant in 50%. The likelihood of progression to RD is between 5-20%. Macular schisis can be differentiated from cystoid macular edema by absence of staining on fluorescein angiography and split in nerve fiber layer on OCT. **Fundus Autofluorescence will show hypoautofluorescent areas corresponding to the *spoke wheel* pattern of folds radiating from fovea. (Fig 7B)**

On **OCT**, a split in neural retina can be demonstrated **at the macula (Fig 7C)** ERG is diagnostic with the typical wave form being "negative" where the "b" wave amplitudes are reduced with relatively better "a" wave amplitudes and b/a ratio being < 1.0. **(Fig 7D)**

Management includes genetic counselling,, topical dorzolamide may help in reducing fluid levels. Laser as an adjuvant or preventive treatment can be used for peripheral schitic changes with breaks. Surgery is recommended for non-resolving vitreous hemorrhage which can happen due to rupture of vitreous veils and for retinal detachments.

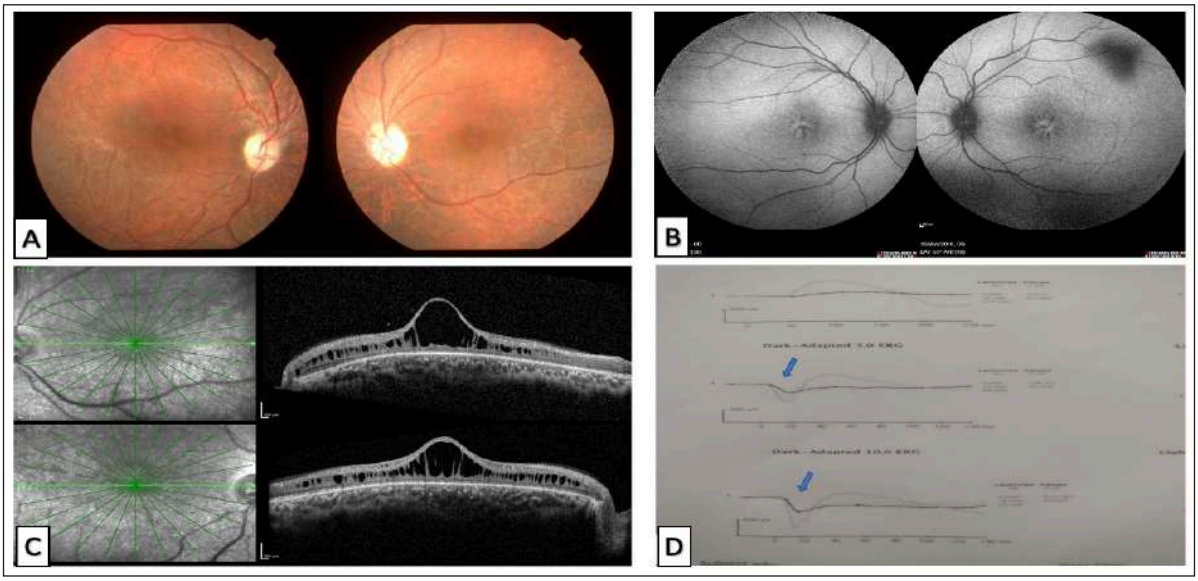

Fig 7. (A) Fundus photograph of X-linked retinoschisis with foveal cysts in a "spoke wheel" pattern. (B) Fundus Autofluorescence showing hypoautofluorescent areas showing spoke wheel pattern of folds radiating from fovea. (C) Spectral domain optical coherence tomography demonstrating the splitting of the inner and outer retinal layers. (D) Electroretinogram showing typical electro negative (arrow) waveforms in scotopic responses.

II. OTHER IRDs WITH RELATIVE MACULAR SPARING:

- Retinitis Pigmentosa
- Choroideremia
- Congenital stationary night blindness (CSNB)
- Gyrate Atrophy

Rod cone dystrophies:

1. Retinitis Pigmentosa

Retinitis Pigmentosa (RP) is the most common IRD with a prevalence of approximately 1:4000 worldwide and affects predominantly rod photoreceptors.[8] The presenting features include night vision abnormalities and progressive visual field loss due to photoreceptor cell death. They can occur as typical RP or have a syndromic association. The fundus is usually characterized by bone spicules, attenuated vessels, and waxy pallor of the optic nerve which are important signs of typical RP (**Figure 8A**).[3] Optical coherence tomography shows decreased thickness of the outer nuclear layer and loss of the external limiting membrane (ELM) and ellipsoid zone. Other associated features can be complicated cataract, cystoid macular oedema (CME) and epiretinal membrane.[8] (**Figure 8B**) Usually, CME in RP doesn't require any intervention, however, it may respond to carbonic anhydrase inhibitors (CA) inhibitors and/ intravitreal steroids.[9] Electroretinogram in RP shows early and severe impairment of pure rod responses with a dramatic decrease in amplitude and implicit times of both a and b-waves. In advanced RP, patients have extinguished rod and cone responses (**Figure 8C**).[8]

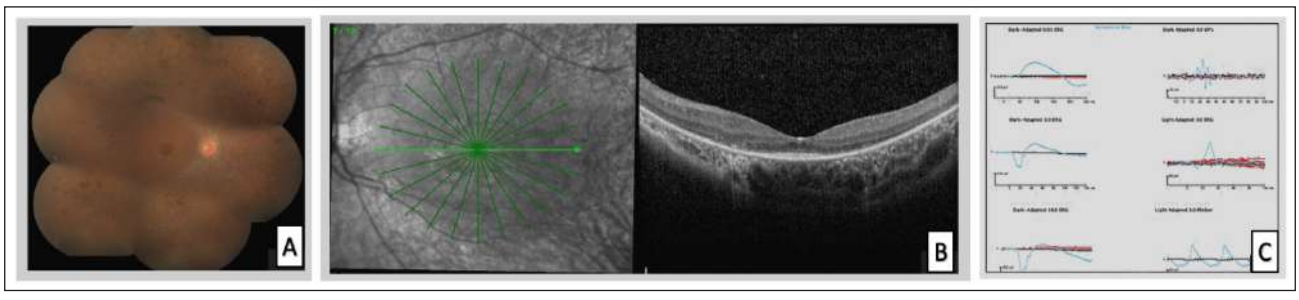

Figure 8 (A): Fundus photo in retinitis pigmentosa (RP) showing bone spicules in the mid periphery and attenuated arterioles. (B): Optical coherence tomography scan through the macula showing photoreceptor layer loss sparing the fovea. (C) Electroretinogram showing extinguished rod and cone responses in advanced RP.

Some other RP variants include-

A. Sector or Sectorial Retinitis Pigmentosa is a specific subtype of RP characterized by pigmentary changes limited to one or two quadrants of the retina with relatively good ERG responses, and minimal or no progression with time (**Fig 9**A). Patients may be asymptomatic or mildly symptomatic. Optical coherence tomography scans will show loss of perifoveal outer retinal layers (Fig 9B).

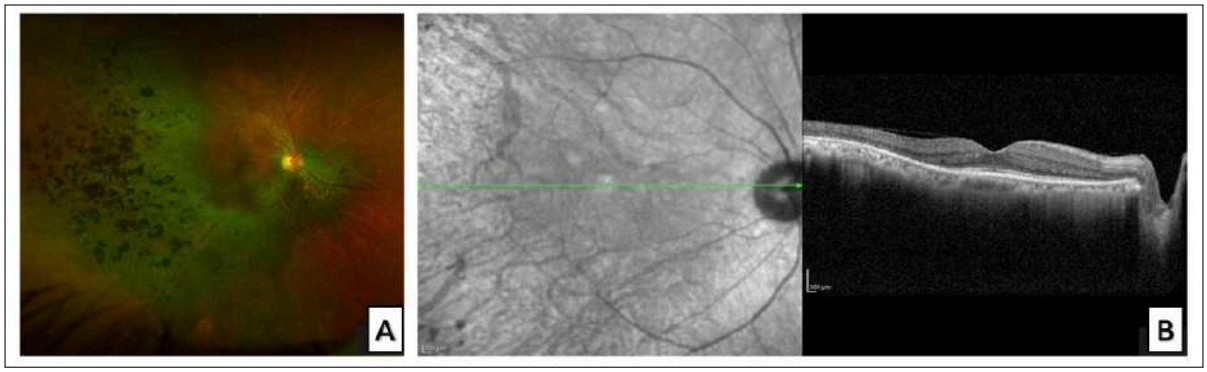

Figure 9 (A): Fundus photo in sectoral retinitis pigmentosa showing bone spicules in the inferotemporal and temporal quadrant (B): Optical coherence tomography scan through the macula showing photoreceptor layer loss sparing the fovea.

B. RP sine pigmento –Here fundus examination may be unremarkable since the characteristic bone spicule like pigmentation is absent, making the diagnosis a challenge (**Figure 10A**).[8] An OCT through the macula may show a perifoveal loss of photoreceptors and RPE (**Figure 10B**). In such cases, an ERG is decisive as it will show changes specific to Retinitis Pigmentosa.

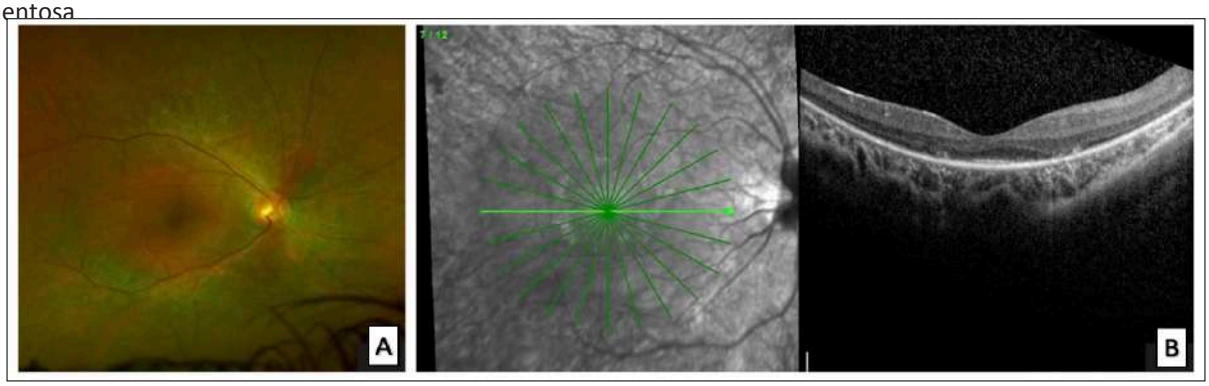

Figure 10 (A): Fundus appearance in retinitis pigmentosa sine pigmento (B): Optical coherence tomography scan through the macula showing photoreceptor layer loss sparing the fovea.

C. Punctata albescens is a form of RP characterized by rounded whitish-yellow deposits in the retina with origin at the level of RPE and located at the equatorial region with similar OT features as in typical RP (**Fig 11(A-B)**).[8] An ERG will show abolition of responses from both rods and cones. Visual prognosis depends on the degree of macular atrophy, which is usually progressive.

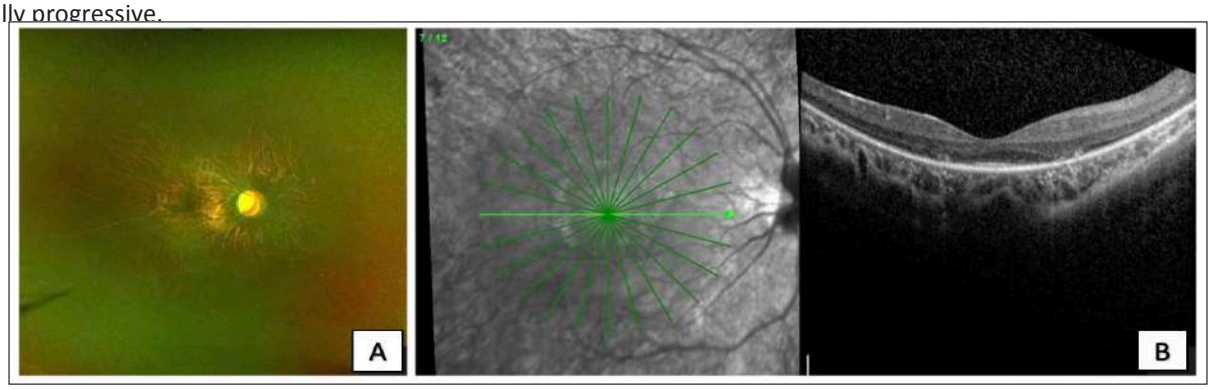

Figure 11 (A): Fundus photo in retinitis pigmentosa punctata albescens showing yellowish-white deposits (B): Optical coherence tomography scan through the macula showing photoreceptor layer loss sparing the fovea.

2. Congenital stationary night blindness:

It includes a group of inherited retinal disorders characterized by infantile onset of nyctalopia and non-progressive retinal dysfunction and is associated with defective rod system transmission.[10] These patients can have a visual acuity within the normal range with or without symptoms of myopia and/or nystagmus. Fundus appearance is normal or may sometimes be altered and is commonly associated with myopia.

Fundus Albipunctatus is a rare type of CSNB with an abnormal fundus appearance and belongs to a heterogenous group of genetically determined flecked retina syndromes. Patients have defective night vision from birth, with multiple white dots visible throughout the fundus, sparing the central fovea (**Figure 12A**).[11] Visual acuity remains good. The inheritance pattern is autosomal recessive. An ERG will show defective scotopic responses (**Figure 12B**).

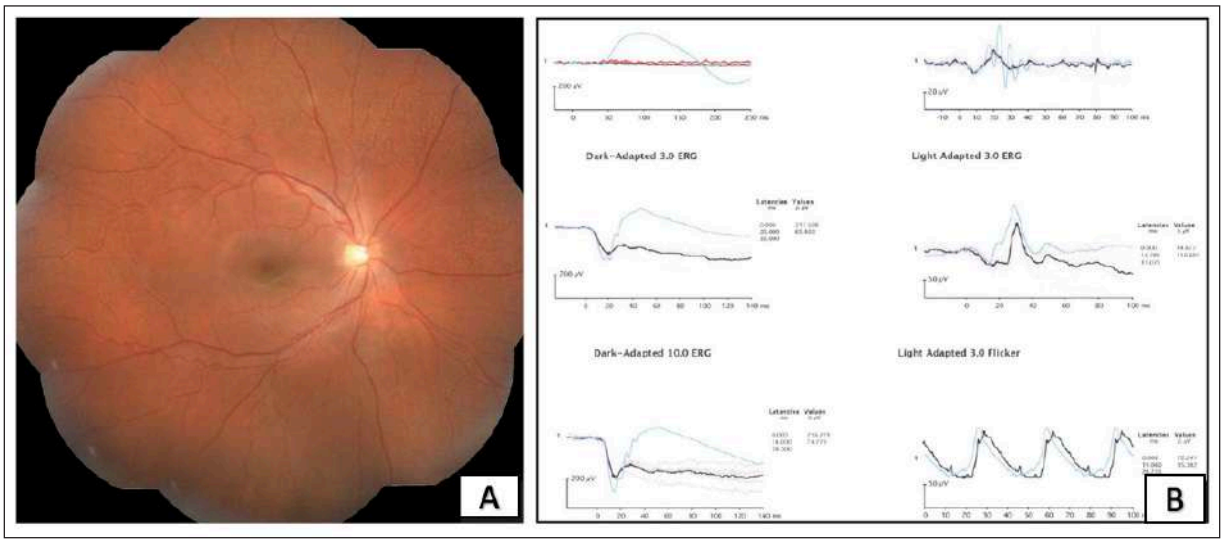

Figure 12 (A): Fundus photo in fundus albipunctatus showing whitish deposits in the retina (B): Electroretinogram showing diminished rod responses and electronegative waveforms in combined responses and normal light adapted cone system response.

Oguchi disease - It is an autosomal recessive form of CSNB and occurs due to disruption in the inactivation of rod phototransduction. Patients present with childhood onset night blindness and a golden sheen on fundus examination. They also exhibit Mizuo Nakamuro phenomenon wherein the fundus appears normal in color after dark adaptation with an appearance of a golden sheen after light exposure.[12] The cause for this is postulated to be elevated extracellular potassium levels generated in the retina in response to an excessive stimulation of rod photoreceptors.

Benign familial fleck retina is a congenital abnormality characterized by multiple yellow-white retinal deposits seen throughout the fundus sparing the macula and is usually bilaterally symmetrical (**Figure 13**).[8] It differs from other fleck retina syndromes as patients are usually asymptomatic, absence of nyctalopia and ERG remains normal.

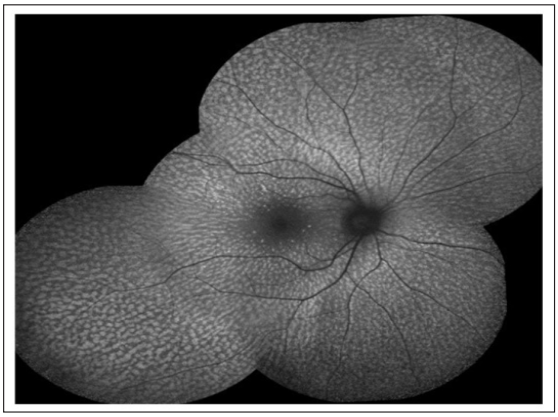

Figure 13: Fundus autofluorescence image in benign flecked retina showing whitish deposits in the retina sparing the fovea.

3. Choroideremia:

It is a rare X-linked chorioretinal dystrophy with progressive, diffuse degeneration of the photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris.[13] It is associated with CHM gene mutation located on chromosome Xq21.2. Nyctalopia usually occurs in the first decade of childhood progressing to peripheral vision loss during teenage. Central vision is usually spared until the fifth to seventh decade of life. Female carriers though generally asymptomatic, may present with mild to moderate nyctalopia. Electroretinography is abnormal in the early stages, characterised by reduction in the scotopic responses prior to the photopic responses[14] which eventually becomes extinguished by middle age. In contrast, carriers usually have a normal ERG pattern, minor changes can be noted in symptomatic carriers.

4. Gyrate atrophy:

Gyrate Atrophy is a rare autosomal recessive retinal dystrophy caused by a deficiency of enzyme ornithine aminotransferase (OAT). It is associated with progressive chorioretinal degeneration, early cataract formation and myopia. Nyctalopia is the usual presenting complaint seen in the first decade of life. It is characterized by circular patches of chorio-retinal atrophy in the peripheral fundus with progressive coalescence in the late stages advancing towards the posterior pole **(Figure 15A)**. **Fundus autofluorescence will show multiple hypo-autofluorescence patches in the corresponding areas, (Fig 15B)** Macula is usually spared until late in the disease.[15] It may be associated with macular oedema and schitic changes for which usually no intervention is required. However, CA inhibitors have been tried in such cases.[16]

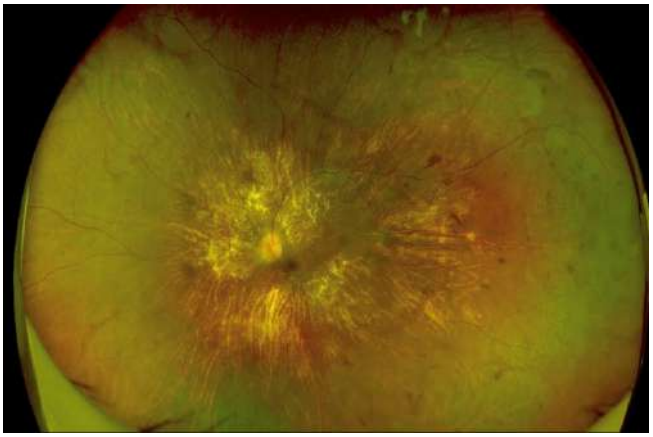

Figure 14 -Wide field fundus image of left eye showing Choroideremia

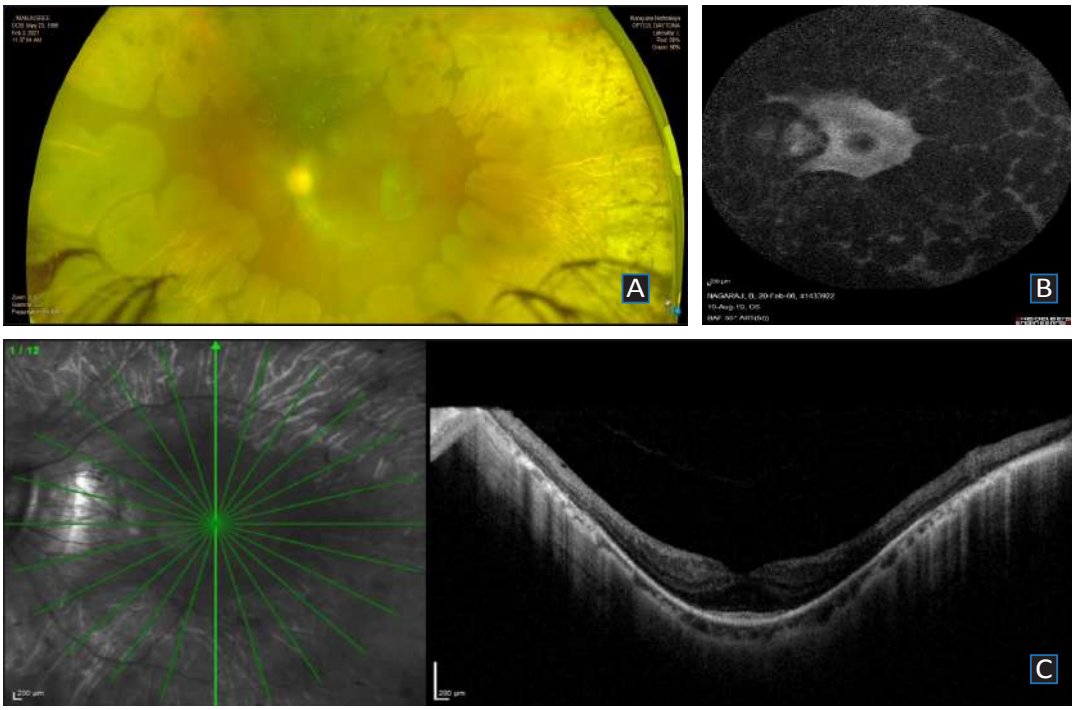

Figure 15:

(A) Wide field fundus image of left eye showing advanced gyrate atrophy,

(B) Fundus autofluorescence of left eye showing multiple hypo-autofluorescence patches corresponding to atrophy sparing fovea,

(C) OCT showing preserved EZ only in foveal region.

Role of genetic testing

The field of genetics is evolving at a very high pace. Eye is second only to the brain as an individual organ in its frequency of involvement in genetic disorders. Almost 50% of paediatric blindness is due to a genetic aetiology.[17] Genetic testing helps to understand the gene responsible for the condition. Once the cause is known; it is easy to find out how far the research related to that gene has come along, and whether a gene therapy available for that particular gene. The literature also guides the clinicians to understand the prognosis of the condition and helps in forming a better treatment and rehabilitation plan for the patient. Families that have affected members can plan for a healthy child with the help of genetic screening.

Summary

Retinal dystrophies are one of the main concerns when it comes to ocular morbidity secondary to retinal disorders and can have varied presentations. It is important to properly diagnose and counsel the patient accordingly in terms of prognosis and life-style modifications which may go a long way and help them lead a productive life. With the advent of better genetic testing methods and gene therapy trials showing some promising results, patients with retinal dystrophies can be offered something better in future.

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Optic disc changes in pathological Myopia

- Dr Isabella V. Wagner[1], Dr Adrian Zarraga Pereda[1], Dr. Christian Draper[1], Dr Syril Dorairaj[1]

[1]Department of Ophthalmology, Mayo Clinic, Jacksonville, Florida, USA

Abstract:

Visual field defects due to optic nerve changes are common in eyes with pathologic myopia (PM). However, it is sometimes difficult to suspect the presence of visual field defects because of the existing deformity of the optic disc. Optical coherence tomography (OCT) is useful to detect structural abnormalities in and around the optic nerve, such as acquired optic disc pits, acquired conus pits, focal lamina defects, and peripapillary intrachoroidal cavitation (ICC).

Key words :
Pathologic myopia · High myopia · Glaucoma · Parapapillary atrophy · Intrachoroidal cavitation · Optic disc pit · Conus pit · Lamina defect

Introduction

Pathologic myopia (PM) causes serious visual field defects which are associated with morphological alterations of the optic nerve due to the extreme elongation and deformity of the globe. The optic disc of the eyes with PM shows various deformities including an extreme tilting, acquired megalodisc, irregular-shaped optic disc, and a large gamma and delta zone of peripapillary atrophy. Because of such deformities of the optic disc, it is difficult to suspect the presence of visual field defects based on optic disc appearance. To overcome this issue, optical coherence tomography (OCT) is a useful tool to detect optic disc abnormalities which may be responsible for visual field defects in eyes with PM, such as

acquired optic disc pits,[1] acquired conus pits, focal lamina defects, [2] and peripapillary intrachoroidal cavitation (ICC). [3,4] This chapter focuses on the association between the optic disc alterations and visual field defects in eyes with PM.

Tilting of the Optic Disc

Tilt and torsion of the optic disc are commonly seen in myopic eyes.[5] Sawada et al. reported that the tilt ratio (defined as the ratio between the longest and shortest diameters of the optic disc) was significantly greater in the eyes with faster progression of visual field (VF) defects than those with slower progression in myopic glaucomatous subjects. [2,6] In eyes with PM, the degree of tilt and torsion increases and in some cases, due to an extreme tilting of the optic disc, the optic disc itself is not visible funduscopically. Because of the tilting, the temporal part of the optic disc is stretched which may facilitate the development of laminar cribrosa defects along the temporal margin of the optic disc. In addition, the retinal nerve fiber is severely bent and distorted along the nasal margin.

Acquired Megalodisc and Small Disc

Various patterns in size of the optic disc are seen in eyes with PM (Figs. 1 and 2). Nagaoka et al. assessed the prevalence of glaucoma in 336 eyes with high myopia, and reported that the proportion of small discs, normal sized discs, and megalodiscs was 64 eyes (19%), 173 eyes (52%), and 99 eyes (29%). Larger disc area was associated with a longer axial length. [7,8] Such large optic disc is also known as “acquired megalodisc.” According to the Beijing Eye Study, “megalodiscs” were defined as discs larger than 3.79 mm^2. [9] The size of acquired megalodisc ranged from 3.79 to 13.96 mm^2 with a mean of 5.39 mm^2 in the study by Nagaoka et al. [7] In multivariate analysis, the prevalence of glaucoma defined by glaucomatous optic disc and glaucomatous visual field defects was 3.2 times higher in megalodiscs than in normal-sized discs or small discs after adjusting for the age. Glaucoma prevalence increased by a factor of 1.39 for each increase of optic disc area by 1 mm^2. In summary, in highly myopic eyes, glaucoma prevalence increased with larger optic disc size beyond a disc area of 3.8 mm^2.The reasons for the increased glaucoma susceptibility in highly myopic eyes with megalodiscs may be histological changes in the lamina cribrosa and in the parapapillary tissue. [10,11] Previous investigations revealed that eyes with myopic axial elongation as compared to eyes with normal axial length showed a marked thinning of the lamina cribrosa. It has been postulated that the thinning of the lamina cribrosa led to

the shortening of the distance between the intraocular compartment and the retrobulbar optic nerve compartment. The parapapillary scleral flange is the continuation of the inner half of the posterior sclera and continues to the lamina cribrosa. In eyes with acquired

megalodisc, the parapapillary scleral flange markedly elongates and thins. Since the parapapillary scleral flange is the biomechanical anchor of the lamina cribrosa, the elongation and thinning of the parapapillary scleral flange may have consequences in the lamina cribrosa including the susceptibility for glaucomatous optic neuropathy.[12] Small optic disc (defined as disc size < 1.51mm^2) was also found in 19% of 336 eyes with high myopia.[7] Different from normal sized disc or megalodisc, the eyes with small optic disc tend to show atypical visual field defects, such as gourd-shaped defects accompanying with both temporal and nasal defects (Fig.3)

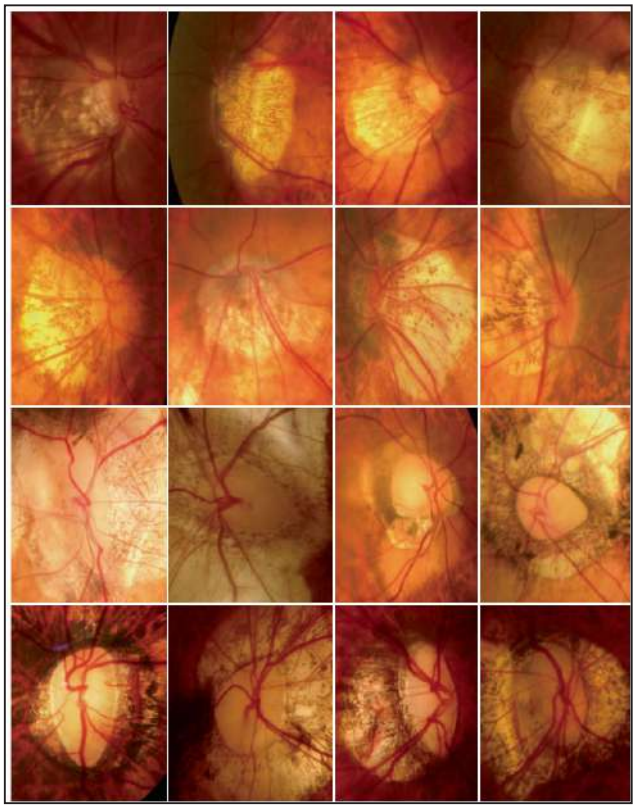


Figure1- Fundus photographs of various shape of the optic disc in pathologic myopia. The upper two rows show extremely tilted discs and small discs. The bottom two rows show acquired megalodiscs and irregular-shaped discs

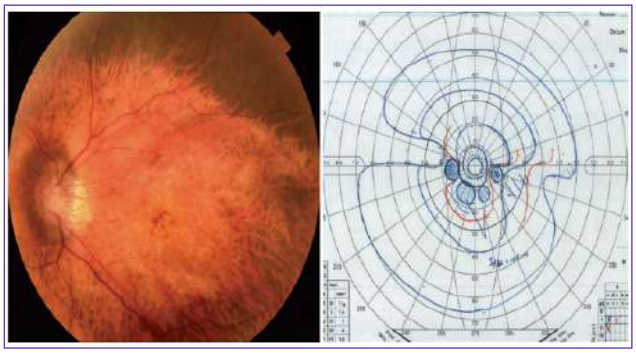


Figure 3-Small optic disc with irregular visual field defects in the left fundus of a 83-year-old man with an axial length of 29.4 mm. (Left) Left fundus shows small optic disc with disc area of 0.51 mm2 . (Right) Goldmann perimetry shows atypical gourd-shaped visual field defects with both temporal and nasal defects

Parapapillary Gamma Zone and Delta Zone(Figure 4)

Jonas et al. histomorphometrically examined the parapapillary region of human eyes. [10] They measured the distance between Bruch's membrane (BM) end and the optic nerve margin ("Gamma zone"); BM end and retinal pigment epithelium (RPE) ("Beta zone"); BM end and the beginning of non-occluded choriocapillaris; and BM end and the beginning of photoreceptor layer. "Delta zone" was defined as a part of gamma zone in which blood vessels of at least 50 µm diameter were not present over a length of >300 µm. Beta zone was significantly larger in the glaucoma group than in the non-glaucomatous group, however, it was not significantly associated with an axial length. In contrast, gamma zone was associated with axial length with an increase starting at an axial length of 26.5 mm. It was not significantly associated with glaucomatous optic neuropathy. In summary, parapapillary gamma zone (parapapillary sclera without overlying choroid, Bruch's membrane and deep retinal layers) was related to axial elongation and was independent of glaucoma. Delta zone was present only in highly axially elongated globes and was not related to glaucoma. Recently they reported that larger gamma and delta zones were correlated with larger optic disc and more marked vertical optic disc rotation, longer disk-fovea distance, higher number of chorioretinal atrophic lesions, and a longer vertical distance between the superior and inferior temporal arterial arcade.[11]

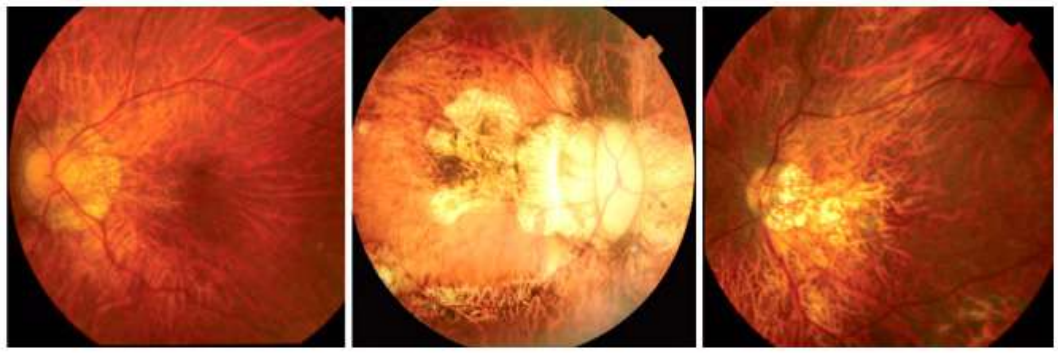


Figure 2- Representative fundus images of normal sized disc (Left, 2.80 mm^2), megalodisc (Middle, 5.15 mm^2) and small disc (Right, 0.66 mm^2) in highly myopic eyes

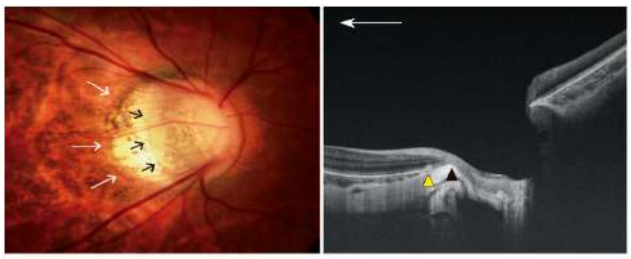


Figure 4-Parapapillary gamma zone and delta zone in the right fundus of a 18-year-old man with an axial length of 28.9 mm. (Left) Right fundus shows parapapillary gamma zone (white arrows; the area without Bruch's membrane) and delta zone (black arrows; no blood vessels
>50 µm diameter within gamma zone). (Right) OCT image shows the margin of gamma zone (yellow arrowhead) and the margin of delta zone (black arrowhead)

Scleral Ridge Temporal to the Optic Disc

Vertically oriented scleral ridge temporal to the optic disc is not uncommon in eyes with PM. This was also reported as type IX staphyloma by Curtin [13]. OCT examinations showed that such changes of scleral curvature occurred at the attachment of the dura mater of subarachnoid space to the peripapillary sclera.[14] Funduscopically, the location of scleral ridge often coincides the border between gamma zone and delta zone (Fig.5). The importance of the scleral ridge lies in a high prevalence of coexisting visual field defects. Ohno-Matsui et al. reported that significant visual field defects (defined as 10% or more loss of V4 isopter and which were not explained by myopic maculopathy or peripheral fundus lesions) were newly developed in 13.2% of 492 highly myopic eyes during a mean follow-up of 11.6 years. [15]An abrupt change of the scleral curvature represented by scleral ridge formation was the only factor significantly associated with a progression of the visual field defects. Akagi et al. reported that the angle of scleral bending at the site of the scleral ridge correlated significantly with retinal nerve fiber layer thickness above the ridge and the visual field defect severity, suggesting that a compression and the thinning of retinal nerve fiber at the scleral ridge may be a cause of visual field defects.[16] Based on these studies, periodical visual field examinations (especially Goldmann perimetry) is strongly recommended for the eyes with scleral ridge

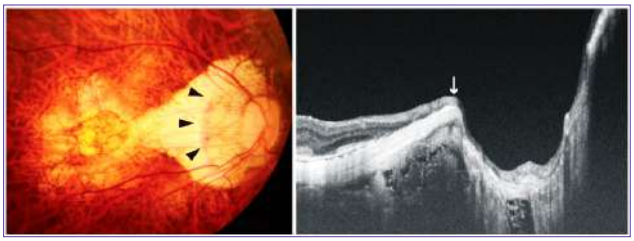
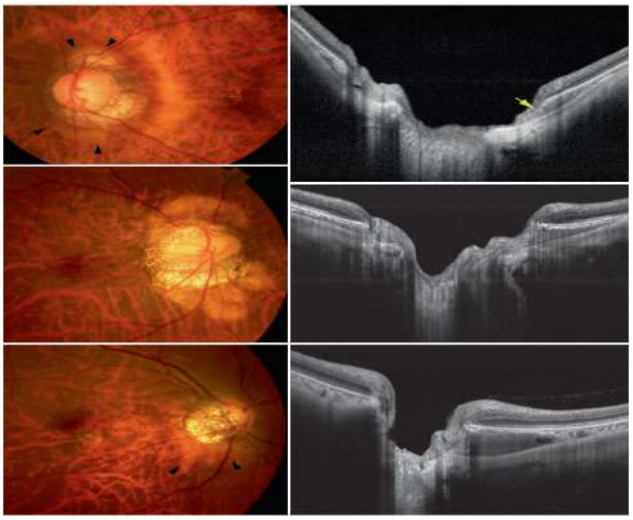


Figure 5-Scleral ridge formation temporal to the optic disc. (Left) Right fundus of a 70-year-old woman with an axial length of 31.1 mm shows scleral ridge (arrowheads) temporal to the optic disc. (Right) A horizontal OCT section across the optic disc shows an acutely protruded scleral ridge (arrow). Retina is severely thinned at and nasal to the scleral ridge. Subarachnoid space is also seen in this image

Peripapillary Intrachoroidal Cavitation (ICC)

Intrachoroidal cavitation (ICC) is a crescent-shaped yellow-orange lesion around the inferior region of the peripapillary myopic conus (Fig. 6). In OCT images, ICC is observed as an intrachoroidal hypo-reflective space (Fig.6). [17,18] However, swept-source OCT shows that some ICC was suprachoroidal separation. [18] In its early development, ICC is just observed as the thickening of peripapillary choroid. ICC most commonly develops lower to the optic disc, but it can also be seen temporal to the optic disc or all around the optic disc. Shimada et al. examined an assessment with the Goldmann visual field test and found glaucomatous visual field defects in 71.0% of eyes with peripapillary ICC.[4] Spaide et al. reported that the thinning or the disruption of the retina at the ICC border area, which may contribute to visual field defects. [18] When the overlying inner retina is defected at the ICC border area, visual field defects similar to glaucoma are found (Fig. 7). In eyes with temporal ICC, a central scotoma is seen.[19] As a cause of ICC, a defect of the border tissue of Jacoby between the choroid and the optic nerve has been suggested.[18]



Figuer 6- Peripapillary intrachoroidal cavitation (ICC) or suprachoroidal separation without cavity formation. (Top row) Left fundus of a 47-year-old man with an axial length of 28.1 mm. Yellowish lesion (arrowheads) is seen around the peripapillary atrophy (PPA). Retinal vein is herniated at around the border of the PPA and ICC. A vertical OCT section across the optic disc shows that the choroid is thickened toward the optic nerve. Sclera is dislocated posteriorly in that area. A disruption of bordering tissue of Jacoby is observed (arrow). (Middle Row) Right fundus of a 60-year-old woman with an axial length of 27.7 mm. Yellowish ICC is seen upper and lower to the PPA. A vertical OCT section across the optic disc shows that the choroid is thickened toward the optic nerve. Sclera is dislocated posteriorly in that area. Choroidal tissue seems to attach the RPE-Bruch's membrane, suggesting that this is more like a suprachoroidal separation. (Bottom Row) Right fundus of a 41-year-old woman with an axial length of 27.8 mm. Yellowish lesion is seen lower to the PPA (arrowheads). A vertical OCT section across the optic disc shows that the choroid is thickened toward the optic nerve. Sclera is dislocated posteriorly in that area. Choroidal tissue seems to attach the RPE-Bruch's membrane, suggesting that this is more like a suprachoroidal separation

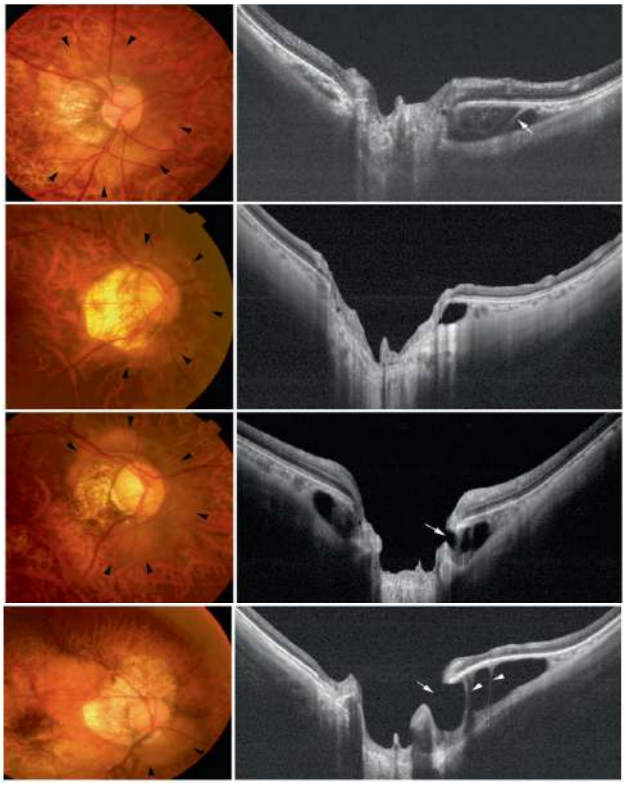


Figure 7-Peripapillary intrachoroidal cavitation (ICC) or suprachoroidal separation with cavity formation. (Top Row) Right fundus of a 54-year-old woman with a refractive error of -14.0 diopters. Yellowish lesion is widely observed around the optic disc and the peripapillary atrophy (PPA). A vertical OCT section across the optic disc shows that the choroid is thickened toward the optic nerve. Sclera is dislocated posteriorly in that area. ICC area shows hypo-reflectance and some strands are seen to course the ICC space (arrow). (Second Row) Right fundus of a 53-year-old man with a refractive error of -10.0 diopters. A yellowish ICC is seen widely around the optic disc and PPA (arrowheads). A vertical OCT section across the optic disc shows that the choroid is thickened toward the optic nerve. Sclera is dislocated posteriorly in that area. Fluid space is seen within the area of ICC. (Third Row) Right fundus of a 57-year-old man with axial length of 29.3 mm. Yellowish lesion is widely observed around the optic disc and the peripapillary atrophy (PPA) (arrowheads). A vertical OCT section across the optic disc shows deep ICCs upper and lower to the optic nerve. Fluid space occupies most of the ICC, and the sclera is dislocated posteriorly. A full thickness defect of the retina is observed at the margin of ICC (arrow) and a direct connection between vitreous cavity and ICC space is seen. (Bottom Row) Right fundus of a 76-year-old woman with axial length of 31.4 mm. Yellowish ICC is observed lower nasal to the optic disc (arrowheads). A vertical OCT section across the optic disc shows very deep ICC lower to the optic nerve. A large defect of full thickness of the retina is observed at the margin of ICC (arrow). A direct communication between vitreous and ICC is seen. Some strands are seen within the ICC (arrowheads)

Optic Disc Pit and Conus Pit

Optic disc pit (Fig.8) and conus pit (Fig.9) are pit-like clefts present near the outer border of the optic disc or within the adjacent scleral crescent in eyes with PM. Ohno-Matsui et al. showed such pit-like clefts were found in 16.2% of highly myopic eyes.[1] These pits occur in eyes with PM due to mechanical expansion of peripapillary region.[1] OCT revealed that the optic disc pits frequently existed in the superior or inferior pole of the optic disc (Fig.8). OCT also demonstrated the presence of conus pits in peripapillary gamma zone (Fig.9), and the invagination of the retinal veins sometimes occurs at the site of conus pits.[20] In addition, the retinal nerve fibers are thinned or completely lost overlying these pits, which causes visual field defects that are similar to glaucoma. Therefore, it is necessary to check the presence of these pits using OCT when we see patients glaucomatous visual field defects in PM.

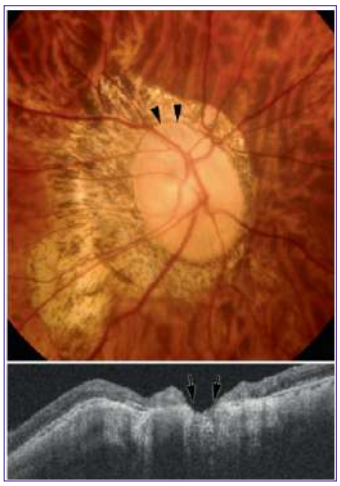


Figure 8- Optic disc pits. Right fundus of a 51-year-old woman with axial length of 32.8 mm. Multiple disc pits (equivalent to lamina cribrosa defects) are seen along the upper border of a large optic disc (arrowheads). A horizontal OCT section across the upper edge of the optic disc shows a defect of lamina cribrosa (between arrows). The retina overlying disc pits is lost

Figure 9-Conus pits in pathologic myopia. (Top Row) Left fundus of a 36-year-old woman with axial length of 32.6 mm. An orange-colored pit (arrow) is seen within a large area of peripapillary atrophy (PPA). An oblique OCT scan across the optic disc shows a conus pit, as a fullthickness defect of sclera (arrow). Overlying retina is herniated into the conus pit. (Middle Row) Right fundus of a 70-year-old woman with axial length of 33.2 mm. Conus pit is not obvious in the fundus image. An oblique OCT scan across the optic disc shows a conus pit, as a full thickness defect of the sclera at the site pointed by an arrow. Overlying retina is herniated into the conus pit. Subarachnoid space (SAS) is seen close to the bottom of the conus pit. (Bottom Row) Right fundus of a 51-year-old woman with axial length of 32.8 mm. A vertically oval-shaped pit (arrow) is observed within a very large PPA. A branch of Zinn-Haller arterial ring is seen to emerge from the upper end of the pit. A horizontal OCT section across the optic disc shows a very deep conus pit (pointed by arrow) nasal to the scleral ridge. Retina is almost absent over the pit

Focal Lamina Cribrosa Defects

Focal lamina cribrosa defects are synonyms of optic disc pits, and acquired optic disc pits are considered an extreme form of focal lamina cribrosa defects. In PM eyes, focal lamina cribrosa defects can be better-detected more than nonhighly myopic eyes (Fig.10) due to the thinning of the prelaminar tissue overlying the lamina cribrosa. In addition, lamina cribrosa is more superficially located in myopic eyes with megalodisc. In PM eyes, focal laminar defects tend to occur at the temporal edge of the optic disc, which may damage papillomacular nerve fiber bundle resulting in the central visual field defect (Fig.10). Focal laminar defects were also found in POAG eyes with high myopia. [21, 22] Jong et al. showed that focal laminar defects in myopic eyes were associated with axial length, maximal length of peripapillary atrophy, and disc tilt angle in multivariate logistic regression analysis. [21, 23]

Enlargement of Subarachnoid Space (SAS)

Subarachnoid space (SAS) is barely visible in non-highly myopic eyes; however, by using EDI-OCT or swept-source OCT, the SAS is visible in eyes with PM through large conus,[14, 24](Fig.11). The SAS is enlarged especially near its anterior surface based on histological study as well as clinical study using OCT.[25] Thus, the SAS in eyes with PM tends to be triangular, with the base toward the eye. Such an increased area exposed to the cerebrospinal pressure and the thinning of the lamina cribrosa and the peripapillary sclera may play a role for the optic nerve damage even within a range of normal intraocular pressure. The sclera overlying the SAS is very thin in some cases, with a short distance between SAS and vitreous cavity. In extreme cases, there is a direct communication between SAS and vitreous.[14] Arachnoid trabeculae, the pia mater, and the dura mater are also visible in some cases.

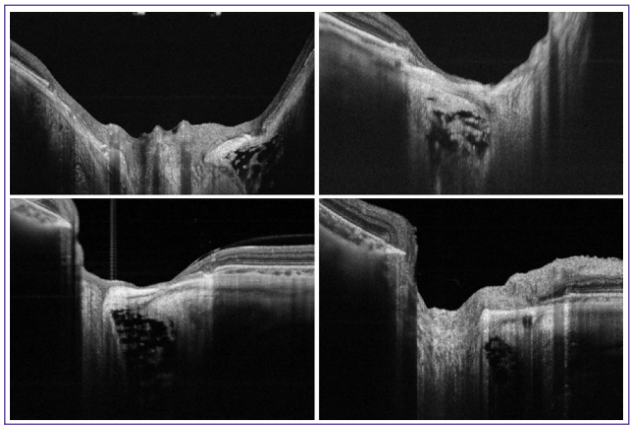


Figure 11-Subarachnoid space (SAS) observed in eyes with pathologic myopia. OCT images show the SAS as a hypo-reflective space, which is triangular with the base toward the eye. The peripapillary sclera is continuous with the pia mater along the inner boundary of the SAS and also continuous with the dura mater along the outer boundary of the SAS. Arachnoid trabeculae is also observed within SAS

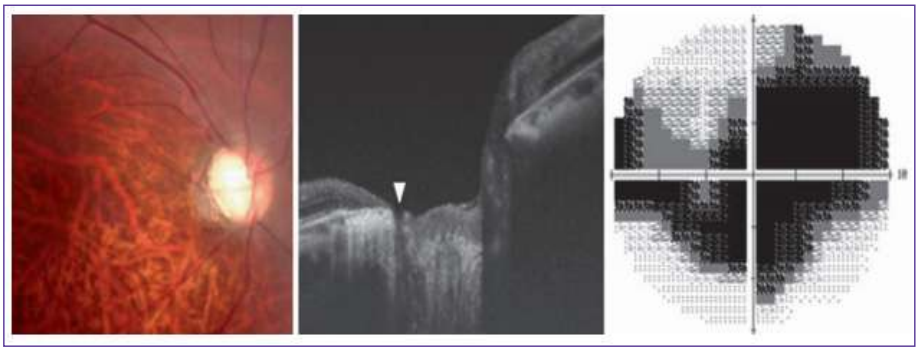


Figure 10- Focal lamina cribrosa defect in an axial myopia. Right fundus of a 46-year-old woman with axial length of 31.3 mm. A horizontal OCT image shows the focal laminar defect at the temporal border of the optic disc. Arrowhead points prelaminar tissue dimpling at the site of the focal laminar defect. Visual field examination using the central 10° visual field (Humphrey Field Analyzer) shows a central scotoma corresponding to the site of the laminar defects

Increased Distance of Zinn–Haller Arterial Circle (ZHAC) from the Optic Disc

Zinn–Haller arterial circle (ZHAC) is an intrascleral arteriolar anastomosis derived from the paraoptic medial and lateral short posterior ciliary arteries (SPCA). The ZHAC is the main blood supply to the optic nerve head at the level of the lamina cribrosa. Because of its intrascleral location, it was difficult to observe in situ. However, in PM eyes, the ZHAC is visible through a large conus by

using ICG angiography and EDI-OCT/sweptsource OCT. [26, 27] OCT shows an entire course of ZHAC from the SPCA emissary to branches toward the optic nerve (Fig.12). The ZHAC is observed by OCT angiography in some cases (Fig.13).[28] In eyes with PM, the ZHAC tends to be away from the optic nerve (Fig.14). The most distant point is the emissary of SPCA into the ZHAC, and thus the ZHAC is some times rhomboid or triangular in shape. In histological study, Jonas et al. reported that the distance between the ZHAC and the optic disc margin reached nearly 3000 µm in extremely myopic eyes.[29] Such an increased distance of the ZHAC away from the optic disc may cause an ischemic insult to the optic nerve.

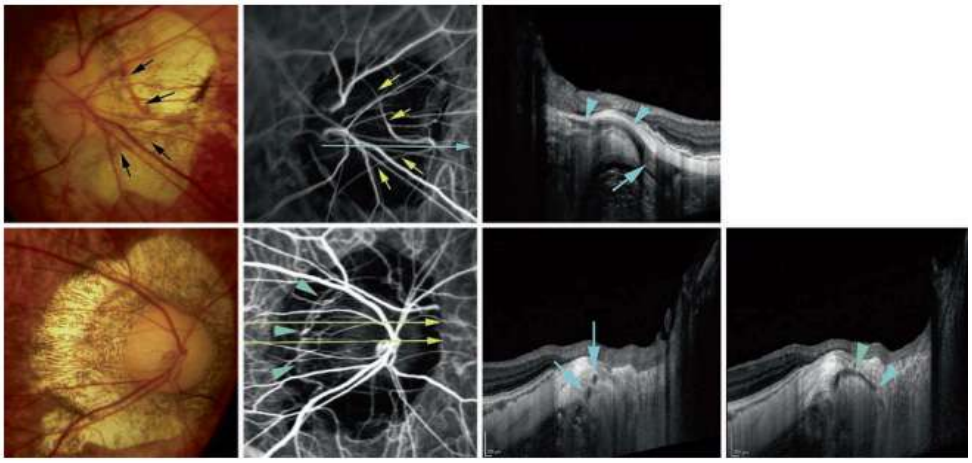


Figure 12-Detection of the path from the retrobulbar short posterior ciliary artery to the Zinn-Haller arterial circle (ZHAC) by OCT and the detection of centripetal branches running toward the optic nerve from the ZHAC both by indocyanine green (ICG) angiography and OCT. (Top Left) Fundus photograph of the left eye of a 55-year-old man with an axial length of 31.2 mm. A large temporal conus is observed. Blood vessels suggesting the ZHAC are seen within the conus (arrows). (Top Middle) ICG angiographic finding at 1 min after dye injection showing the temporal part of the ZHAC with a triangular shape (arrows). A lateral short posterior ciliary artery enters the ZHAC at its most horizontally distant point. A blue line shows the scanned line by OCT. (Top Right) Horizontal OCT scan shows that the short posterior ciliary artery enters the sclera (arrow) and courses toward the ZHAC intrasclerally (along the arrowheads). (Bottom Left) Fundus photograph of right eye of a 68-year-old man with an axial length of 29.7 mm. An annular conus is seen. (Bottom second from the left) ICG angiographic finding at 1 min after dye injection showing multiple vessels consisting of the ZHAC (arrowheads) located temporal to the optic disc within the area of the conus. The scanned lines by OCT are shown as yellow lines. (Bottom third from the left) Upper horizontal OCT scan shows two hypo-reflective circular areas (arrows) corresponding to vessels of the ZHAC. (Bottom Right) In the lower section, the centripetal branch (arrowheads) toward the optic nerve can be seen

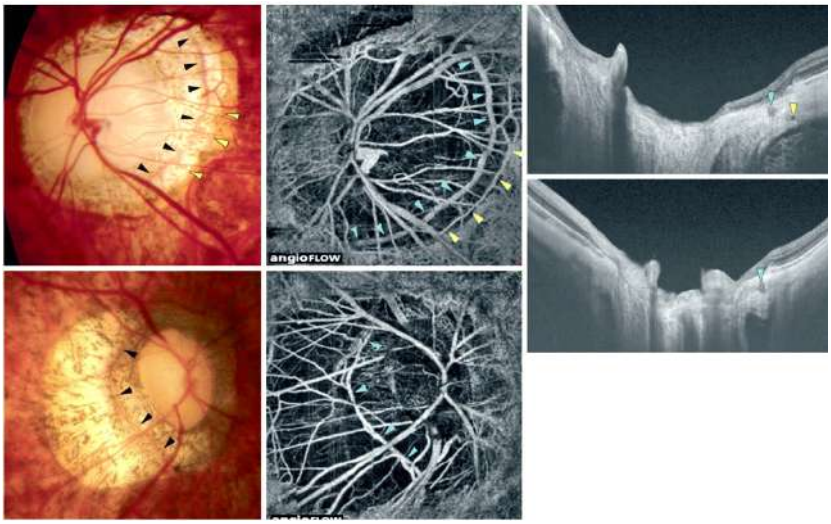


Figure 13- The Zinn-Haller arterial circle (ZHAC) as imaged by optical coherence tomography angiography (OCT-A). (Top Left) In the left fundus, ZHAC (black arrowheads) is detected in the region of the peripapillary conus (gamma zone). Outside of the main arterial circle (black arrowheads), a second arterial circle is present (yellow arrowheads). (Top Middle) On OCT-A image, a double ring of ZHAC consisting of a wider ring (blue arrowheads) and a narrower ring (yellow arrowheads) can be seen. In particular inferior to the optic disc, the wider ring is observed to a wider extent than on the fundus photo. (Top Right, upper image) In a horizontal section of the swept-source OCT image, cross sections of the inner (wider) artery of the ZHAC (blue arrowhead) and the outer (narrower) artery of the ZHAC (yellow arrowhead) are visible within the peripapillary sclera in the region of the parapapillary gamma zone. The outer artery of the ZHAC as compared to the inner artery is located deeper in the sclera. (Top Right, lower image) In a vertical section of swept-source OCT image, a cross section of the inner artery of the ZHAC is visible within the scleral stroma (arrowhead). (Bottom Left) In the right fundus, the ZHAC (arrowheads) is visible in the region of the peripapillary conus (parapapillary gamma zone). (Bottom Right) On the OCT-A image, the ZHAC (arrowheads), in particular its small branches, are more clearly seen than on the fundus photo

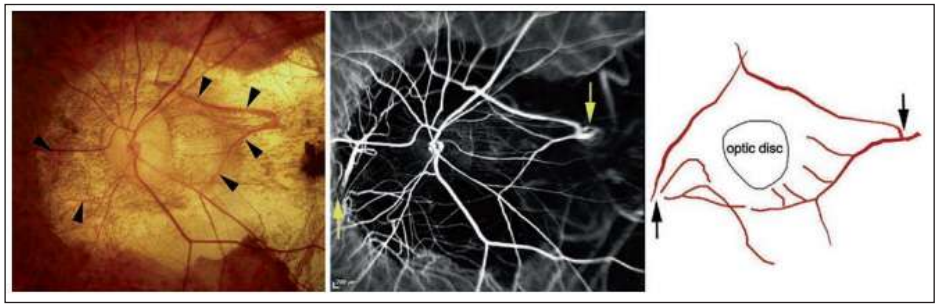


Figure 14-A rhomboid shape of the Zinn-Haller arterial circle (ZHAC) in pathologic myopia observed by indocyanine green (ICG) angiography. (Left) Left fundus of an 84-year-old woman with an axial length of 30.0 mm. A large annular conus is observed. Blood vessels suggesting the ZHAC are seen within the conus (arrowheads). (Middle) ICG angiographic finding at 1 min after the dye injection showing a rhomboid-shaped ZHAC surrounding the optic disc. Medial and lateral short posterior ciliary arteries enter the ZHAC at the points shown by arrows. (Right) Schematic drawing of ICG angiographic finding. The ZHAC is drawn in red and has a horizontally long rhomboid shape. The medial and lateral short posterior ciliary arteries enter the ZHAC at the most horizontally protruded point (arrows). Centripetal branches running toward the optic nerve from the ZHAC are shown.

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Botulinum Toxin and Fillers for Oculofacial Aesthetic Rejuvenation

- Dr Moupia Goswami Mukhopadhyay, DNB
Dept of Ophthalmic Plastic Surgery, Narayana Nethralaya, Bangalore

Abstract

Injectables namely Botulinum toxin A and soft tissue fillers have become popular modalities of non-invasive periocular and facial rejuvenation worldwide. The goal is to carry out rejuvenating procedures that restores balance and proportion to the ageing face and help the person to look his/her best by hiding signs of chronological ageing. The purpose of this article is to present a comprehensive review on cosmetic uses of these injectables.

Key words :
Botulinum Toxin , Hyaluronic Acid Fillers

Introduction

The desire to enhance cosmetic appearance and to look more beautiful has been a human requirement over many centuries. In this 21st century, that perfect, aesthetic facial beauty is no longer a mere dream but is now a goal that can actually be achieved with the availability of botulinum toxin, fillers and other minimally invasive interventions. [1]

Ophthalmologists are uniquely positioned to perform certain aesthetic procedures. We often get queries regarding dark circle and blemishes around the eyes. Being ophthalmologists and microsurgeons, we have greater insight into periocular anatomy and have better hand control[1]. Thus, aesthetics can easily be an integral part of an ophthalmologist's practise.

The recent published statistics report by ISAPS (International Society of Aesthetic Plastic Surgery) reported that nonsurgical procedures (primarily fillers and hair treatments) continued to increase, but by lower proportions than seen in previous years[2](5.7% in 2020, compared to 7.6% in 2019).Botulinum toxin is the most requested minimally invasive cosmetic procedure worldwide.

Pathophysiology of the ageing face

Ideal normal facial appearance comprises of facial balance, harmony and favourable proportions. Ageing of face is inevitable resulting in progressive deterioration, volume loss and stretching of tissues as age increases .

Our face creates strong impression on others, which is known as emotional attributes. A slim youthful face in females makes her look more feminine and attractive (positive emotional attribute) . On the other hand, a saggy face with lots of wrinkles makes one look tired and angry (conveying negative emotional attribute).

Factors that determine the ageing process include –

1. **Genetic factors** – Accounts for 1/3 of the ageing pattern.
2. **Race** – People with darker skin have greater amount of pigmentation and thicker dermis . This delays fine lines, wrinkles and pigmentary changes in the skin. Compromised mid facial skeleton (malar hypoplasia and negative corneal vector) leads to premature mid facial ageing. This is very common in Indian subcontinent.
3. **General health and life style** - Nutrition, sleep, life style, fitness and stress contribute to 2/3 of the ageing process. Alcohol, smoking , sudden weight gain and weight loss , facial animation and malnutrition accelerates the ageing process of the body.

The ageing changes are seen in all layers of the face –

1. **Skin quality and elasticity of the face** – As we age, the cells divide slower. The elastin and collagen in the dermis breaks down and thus dermis becomes thinner, skin sags. There is progressive loss of water content and fragmentation of collagen leading to thin skin with loss of tone. Years of frowning and smiling (contraction of underlying muscles) leads to formation of wrinkles around the eyes and the forehead. Wrinkles and folds form around the mouth and the nose. Excess skin is seen around the jawline and under the chin. Hyperpigmentation (melanocyte proliferation) and age spots are seen on the skin.

2. **Facial mimetic muscles** – Muscles / musculocutaneous insertions lose tone and stretch, which in turn contributes to sagging and redundancy.

3. **Facial fat pads** – The fat pads of the face acts as a cushion and gives volume and youthfulness to the face. The superficial and deep fat pads are uniform in distribution in youth. As age progresses, the fat pads are reabsorbed (shrink)and redistributed (shift) which gives hollowness in the temples and mid face (inframalar cheek and infraorbital tear trough). Descent of fat pads increase fullness and sagging in the lower face creating a double chin. The volume and definition of lips decrease. The lips become thin and corners droop. The major fat pad compartments in the face are – nasolabial fat pad, cheek fat pad, forehead and temporal fat pad, orbital fat pad and jowl fat pad.(Fig 1)

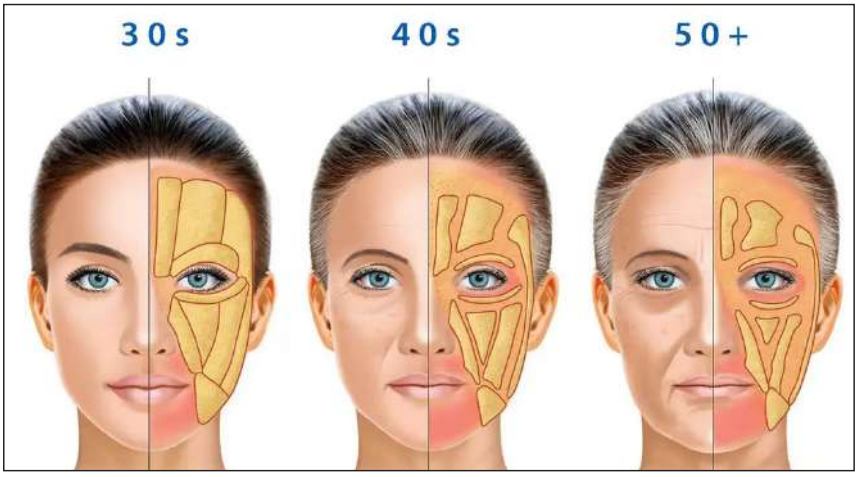

Figure 1. Due to ageing , there is loss of superficial and deep fat fads in the face , which contributes to volume loss and sagging of the face .Photo credit – Allergan .

4. **Retaining ligaments** – These are present where septal barriers and fat compartments meet. In the periorbital region, they include the orbital retaining ligament (orbital septum) and the lateral orbital thickening (zygomatic ligament).Other important ligaments of face include mandibular ligament and parotido masseteric ligament. These ligaments become lax with age.

5. **Bone** – Lastly, the bones of the facial skeleton also get resorbed with age , making the structure of the face becomes more hollow , especially around the eyes , cheeks and chin. Structural support reduces causing the facial tissues to sag.

In this article, we will be discussing two very popular ,revolutionary injectable treatment for facial aesthetics and rejuvenation , namely Botulinum Toxin and Hyaluronic Acid Fillers .

BOTULINUM TOXIN

In 1987, while treating patients for essential blepharospasm, Jean Carruthers , an ophthalmologist , noted that those patients had significant improvement of glabellar rhytids. Jean and husband Alastair Carruthers, dermatologist in 1992, researched and published on safety of botulinum toxin for dynamic rhytids, ushering in an era of cosmetic uses of Botulinum Toxin.

Botulinum toxin is produced by the gram positive, anaerobic bacteria, Clostridium botulinum serotype A .It's main cosmetic use is to smoothen wrinkles and rhytids in the face caused due to facial expressions, which are called as dynamic wrinkles. It is also used for contouring and lifting the face. Some of the indications are US Food and Drug Administration approved, while others are off label.

Mechanism of action

Botulinum toxin A inhibits the presynaptic release of acetylcholine at the neuromuscular junction, diminishing the contraction of the muscle unit. This selectively weakens the overlying rhytids .

Figure 2 . Photos of bottles of currently available brands of Botulinum Toxin Type A .

Various currently available Botulinum Toxins

The two most potent and widely used Botulinum Toxin are type A and type B. The three FDA approved cosmetic Botulinum Toxin – A drugs are onabotulinum toxin A (Botox Cosmetic), abobotulinum toxin A (Dysport) and incobotulinum toxin A (xeomin) Botulinum toxin type B is rimabotulinum toxin B (Myobloc), not currently available in India .(Figure 2)

Biosimilars of Botulinum toxin are also available in India. A recently FDA approved Revance therapeutics , brand Daxxify, has shown much long lasting result, about 6 months, as compared to currently available botulinum toxins.

Reconstitution -

Botox, Dysport and Xeomin are available as powder and is reconstituted with 0.9% saline. Botox is commonly reconstituted with 2.5 cc of preserved saline for 100 U bottle and 1.25 cc for a 50 U bottle , yielding 4U per 0.1 cc.

Cosmetic indications and Dosage

Dynamic wrinkles caused by persistent muscle contractions are the main aesthetic indications of Botulinum Toxin (BT).

Table 1 . Consensus Recommendations Regarding Onabotulinumtoxin A Treatment of the Upper Face

Indication	Target Muscle	Preferred Injection Level	Injection Points (n)	Typical OnabotulinumtoxinA Dose per Injection Point	Typical Total Dose of OnabotulinutoxinA
Glabellar lines	Procerus, corrugator supercilii, orbicularis oculi, depressor supercilii	Intramuscular	3 to 7	2 to 4 U	12 to 40 U; doses as low as 8 U may be appropriate for some patients
Horizontal fore- head lines	Frontalis; consider interactions with procerus, corrugators, and orbicula- ris oculi in dosing, and effect on shape of the brows	Intramuscular or intracutaneous	4 to 8 (nonmicro droplet) 8 to 20 (microdroplet)	2 to 4 U (nonmicrodroplet) 0.5 to 1.5 U microdroplet)	8 to 25 U
Lateral canthal lines	Orbicularis oculi; uppermost injec- tion point can also provide brow elevation	Intracutaneous	1 to 5 per side	1 to 4 U	6 to 15 U per side; doses as low as 4 U may be appropriate for some patients
Brow elevation	Lateral: orbicularis oculi; injection point is superior to the uppermost injection point for lateral canthal lines, and typically at the hairline of the eyebrow Medial: procerus, corrugator supercilii, depres- sor supercilii, orbicularis oculi	Intramuscular	Lateral, 1 to 2 per side Medial, 1 to 2	Lateral: 0.5 to 1 U Medial: 0.5 to 4 U	1 to 6 U

Figure 3.

External photograph showing deep lateral canthal rhytides(Crows feet) .

A – before Botulinum Toxin Injection.

B – 5 days after treatment , when rhytides have vanished

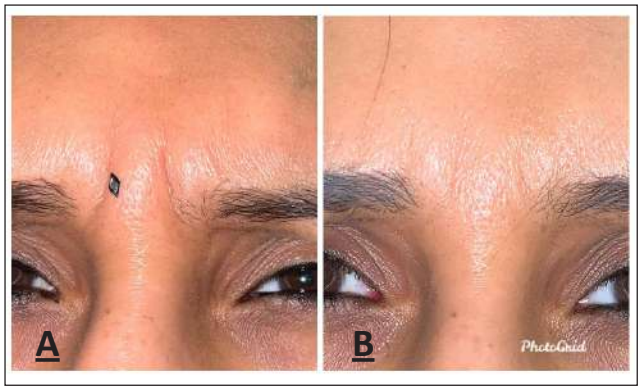

Figure 4.

External photograph showing vertical glabellar lines between the medial head of both eyebrows.

A – Before treatment,

B – After treatment with Botulinum Toxin

Table 2. Consensus recommendation regarding treatment of Midface with Onabotulinum Toxin A (adapted from Hema Sundaram et al)

Indication	Target Muscle	Preferred Injection Level	Injection Points (n)	Typical OnabotulinumtoxinA Dose per Injection Point	Typical Total Dose of OnabotulinutoxinA
Infraorbital rhytides	Orbicularis oculi	Intracutaneous	1 to 3 per side; microdroplet technique may be beneficial	0.5 to 2 U	0.5 to 2 U per side
Eye opening (lowering of inferior cili- ary margin)	Orbicularis oculi	Intracutaneous	1 per side; midpupillary line	0.5 to 1 U	0.5 to 1 U per side
Nasal flare	Dilator nasalis (alar portion of nasalis) Medial portion of levator labii superio- ris alaeque nasi may also be considered	Intramuscular	2	1 to 2 U	1 to 4 U
Nasal tip elevation	Depressor septi nasi	Intramuscular; often ancillary to fillers	2 to 3	2 to 4 U	4–8 U; doses as high as 10 U may be appropriate for some patients
Nasal oblique lines (bunny lines)	Nasalis; levator labii superioris alaeque nasi and depressor nasi septi should also be considered	Intramuscular	2 to 3	2 to 4 U	4–8 U; doses as high as 10 U may be appropriate for some patients
Excessive gingival show (gum- my smile)	Convergence of leva- tor labii superioris alaeque nasi and zygomaticus minor with insertion of levator labii supe- rioris	Intramuscular	1 to 2 per side	0.5 to 2 U	1 to 4 U; doses as high as 8 U may be appropriate for some patients

Table 3. Consensus recommendation for treatment of Lower Face with Onabotulinum Toxin A

Indication	Target Muscle	Preferred Injection Level	Injection Points (n)	Typical OnabotulinumtoxinA Dose per Injection Point	Typical Total Dose of OnabotulinutoxinA
Depressor anguli oris overactivity	Depressor anguli oris	Intramuscular	1 to 2 per side	2 U	2 to 4 U per side; some panelists limit dose to 2 U per side
Mentalis overactivity	Mentalis	Intramuscular	1 to 4 per side	2 to 3 U	4 to 10 U
Masseter overactivity	Masseter	Intramuscular	1 to 5 per side	5 to 15 U	15 to 40 U
Perioral rhytides	Orbicularis oris	Intracutaneous; ideally, intradermal	2 to 5	0.5 to 1 U	1 to 5 U
Platysmal bands	Platysma	Intramuscular or intracutaneous	3 to 6 per band	1 to 3 U	6 to 12 U per band; maximum dose 60 U

Tables 1,2 and 3 are adapted from Sundaram H et al [3]

Mesobotox –

Microdose quantities of botulinum toxin is injected intradermally at multiple points all over the face to achieve brightness of skin , improvement in skin texture and decrease pigmentation .The microinjection into mesoderm causes sweat glands and sebaceous glands to shrink and atrophy , resulting in smooth clear skin , without weakness of facial movements. In the lower part of the face close to the jaw line , this has a lifting effect , as it cancels the downward pull of platysma

Main contraindications are pregnancy, lactation, allergy to eggs. Relative contraindications are disorders of neuromuscular junction like Myasthenia Gravis, Eaton Lambert syndrome , multiple sclerosis , amyotropic lateral sclerosis , concomitant use of aminoglycoside antibiotics.

Injection technique

After detailed consultation and discussion with the patient to bring out the desires of the patient , I assess the face of the patient both at rest as well as while the patient is smiling ,talking and at maximum eyebrow elevation and maximum frown (dynamic wrinkles). I mark the points with marking pencil and prefer to use local anesthetic cream or ice to numb the injection points.

In order to treat the horizontal forehead expression lines , a use a total of 15-20 U of onabotulinum toxin , in a wide M pattern. In the glabellar area , I mark 3 or 5 points depending of the severity of wrinkles and muscle strength. I inject 4U at each point. In the crow feet area , I inject 4U at each of the three injection points on each side , in the lateral orbicularis muscle .Thus a total of 12 U on each side. We should be away from the lateral canthus and the needle should direct towards the orbital rim . We should not chase the lowermost wrinkles in the crow feet and not go below the zygomatic arch, as there is risk of injecting into the zygomatic major and minor muscle and cause drooping of the corner of the mouth.

I slightly titrate the injection points depending on the pattern of the wrinkles. Consent form for photography of the face and for the procedure are signed beforehand .

Post procedure instructions

1. Not the massage the treatment area for atleast 4 hours after the procedure
2. Avoid bending down or participating in tiring physical activity on the same down
3. Results of treatment may take up to 4-5 days to become apparent . Followup review after 2 weeks.

Some Potential Adverse Events from Aesthetic Use of Botulinum Toxin Type A*

Upper face and midface

–Asymmetry

–Ptosis of eyebrow or eyelid

–Unmasking of preexisting, compensated eyelid ptosis (weakening of frontalis)

–Impairment of eyelid function/ocular physiology (weakening of orbicularis oculi)

–Lower lid retraction/scleral show (weakening of orbicularis oculi)

–Lip ptosis (weakening of lip elevators when addressing nasal indications)

–Atrophy

Lower face

–Asymmetry

–Oral motor insufficiency, e.g., impaired ability to raise or lower the lip

–Impairment of dental show in animation (smiling)

–Impaired muscular support of lower face

–Dysphagia (when targeting platysma)

–Neck weakness (when targeting platysma)

–Dry mouth (when targeting platysma)

FILLERS

As we age, the loss of soft tissue volume in the periocular area and face, needs to be replaced to give a youthful appearance . Several types of injectable soft tissue fillers exist , which when used appropriately , creates facial balance and harmony. Soft tissue fillers are complimentary to botulinum toxin – fillers replace lost volume and botulinum toxin relaxes wrinkles.

Types of Fillers

Fillers are classified as biodegradeable and non biodegradable fillers .Examples of biodegradable fillers are collagen, hyaluronic acid, alginate, poly L lactic acid and calcium hydroxylapatite. Silicon, polyacrylamide and polyalkylimide are examples of non biodegradable filler.

1. Autologous fat – is the oldest injectable filler. Although abundant and biocompatible , its permanency varies [4].Various techniques for harvesting , processing and injecting on the face have been described. Depending on the processing, harvested fat has been classified into macrofat, microfat, superficial enhanced fluid fat (SEFF) and nanofat . SEFF and nanofat is used for periocular rejuvenation.[5] SEEFI and M-SEEFI techniques are popular for skin ageing of periocular and perioral regions [6] . Main disadvantage of fat grafting is donor site morbidity.
2. Hyaluronic acid gel – offers a versatile and safe method of replacing soft tissue lost from upper lid brow complex and tear trough. It can also correct contour defects and provide support and structure to the face.The advantages are in office procedure , no donor site morbidity , proven safety profile and instant reversibility with hylase , if required.

   Hyaluronic acid (HA) is a natural polysaccharide polymer present in human dermis. Due to its chemical structure and hydrophilic nature, it plays an important role in maintaining hydration within tissues.

   The currently popular hyaluronic acid fillers are produced by bacterial fermentation (streptococcus strains) and stabilised by cross linking to increase its longevity. The various products differ in their cross linking methods, concentration and particle size. Structurally the hyaluronic acid fillers are similar to native tissue, providing excellent biocompatibility and good tissue integration. Brands like Juvederm and Restylane have their unique technology, to meet specific needs. Vycross technology of Juvederm is a proprietary mix of low and high molecular weight hyaluronic acid, combined with crosslinking , results in a tightly crosslinked gel. This results in greater resistance to degradation and minimal gel expansion . Gel hardness (G') and cohesivity is customised to give optimum lift and mouldability. NASHA (Non Animal Stabilised Hyaluronic Acid , firmer in nature , pronounced lifting capacity) and OBT (Optimum balance technology ,soft, flexible gel for dynamic areas of the face) are patented technology of Restylane for various indications for the face.

   Now a days, most HA fillers have lidocaine mixed in the gel to reduce procedural pain.

   Other brands of HA fillers are Belotero (Merz),Teosyal , Emervel . Some other brands available in Indian market are Menarini , Shypha and Princess fillers.
3. Radiesse (Merz Aesthetics) – consists of calcium hydroxyapatite that serves as a scaffold for native collagen growth.It is highly viscous and therefore injection has to be deep. Lasts for 9 to 18 months or more.Nodule formation is possible.
4. Sculptra (Galderma) – is an injectable poly-L-lactic acid , constituted from microspheres in powder form. Stimulates fibroblasts and enables type 1 collagen formation . Nodule formation is possible, thus deep injection is advised. This was first approved for facial lipodystrophy syndrome, commonly seen in HIV.

Common Indications

HA fillers is used to correct volume deficiency and sagging of the entire face. The full face has to be taken as a whole which assessing the face and making a treatment plan .

Ageing changes in the face makes the face look tired, sunken and sad. These are called as negative attributes. It is essential to treat the negative attributes first before enhancing the positive attributes. This theory was proposed by Dr Mauricio de Maio, plastic surgeon from Brazil.

Indications in the face would be –

1. Forehead and glabella – Horizontal forehead wrinkles and wrinkles between the two eyebrows (in the glabellar area), smoothens with botulinum toxin Injection. Wrinkles which are very deep and present even at rest , needs fillers .

2. Temples – As we age, fat loss occurs in the temples which makes it concave and hollow. Filler in this area restores the youthful convexity as well as raises the tail of the brow to open up the eyes.

Upper eyelid filling and contouring - HA fillers are particularly successful in patients with medial /generalized upper eyelid hollowing or significant post blepharoplasty upper eyelid show. Upper eyelid hollow or superior sulcus deformity has been classified into 4 types –

- ❖ Type 1 , medial A shaped hollow
- ❖ Type 2 , generalised hollow
- ❖ Type 3 ,post blepharoplasty generalised volume loss with extra skin
- ❖ Type 4 , upper eyelid hooding with subbrow deflation

In all the above types , preperiosteal injection with serial puncture technique , gave good results.[7]

3. Infraorbital hollow and tear trough deformity – In youth , the lower eyelid starts at tarsal insertion and flows in a smooth convexity all the way down to the nasolabial fold and buccal region. The lid cheek junction is short and smooth and there is no distinction between eyelid and cheek.

As we age, loss of fat and breakdown of collagen and elastin occurs leading to volume loss or deflation and infraorbital hollow. This creates a shadow effect, which is often perceived as dark circles.

HA fillers are most often recommended in the tear trough area , as any undesired result can be reversed with injection of hyaluronidase. Low viscosity products are preferred in this area as the skin is thin. Injection can be performed with needles or blunt cannulas. Multiple entry points with either micro bolus (0.01 to 0.02ml per point) or retrograde product delivery along the inferior orbital rim is preferred.This is followed by gentle massage with finger or cotton buds.

HA fillers helps in shortening of lid cheek junction and improvement of dark circles occur through tissue expansion. The duration of results in most patients can be expected to be 1 or even 2 years.

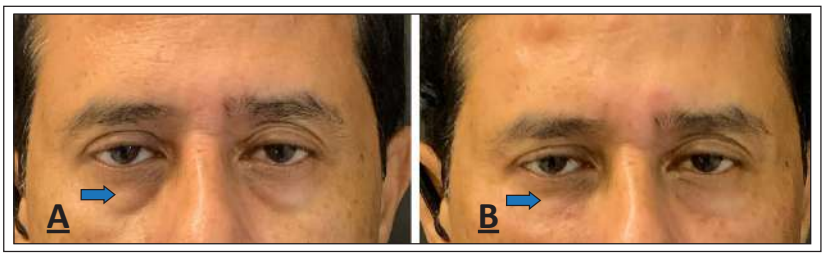

Fig 5. External photograph showing correction/camouflage of Eyebags with fillers.
A – Before treatment .
B – Immediately after treatment

Cheek bones and cheek shaping – The malar projection and full cheeks are important hallmarks of facial beauty and youthfulness. Volume loss causes depression in the anterior projection of the cheek , cheek ptosis and malar mounds are seen .

In the upper mid cheek and upper lateral cheek area , volume deficiencies are mostly corrected by injection of high G prime filler at that level. When there is infraorbital hollow, tear trough , mid cheek deficiency and deep nasolabial fold , we start by restoring volume at lateral cheek bone level. This significantly improves both the nasolabial fold and tear trough area .

Fanning technique is used in the entire area and multilayer injections are conducted from deep dermis to muscular layers.

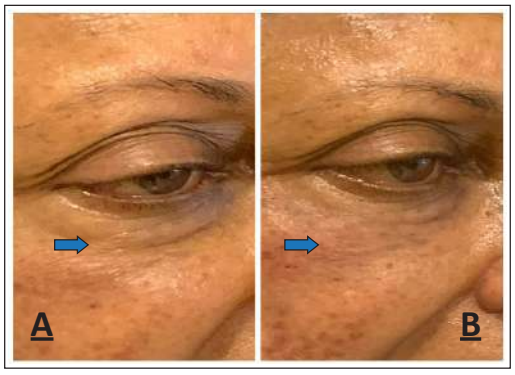

Fig 6. External photograph showing shortening on the lid cheek junction and partial camouflage of eyebag, after treatment with HA filler.
A – before treatment. B – After treatment.

4. **Nose Reshaping –** Reshaping the dorsum of the nose and lifting the tip can be effectively achieved with HA fillers. This is also called as non surgical rhinoplasty.

The nasofrontal angle is filled and its concavity reduced , making the dorsum straight and thus correcting dorsal hump.

Direct injection into the tip of the nose promotes both lifting and projection.

Most dreaded complication during nose shaping is necrosis and blindness.

5. **Nasolabial folds –** are a major indication . Low viscosity HA , is injected in linear retrograde manner , after supporting

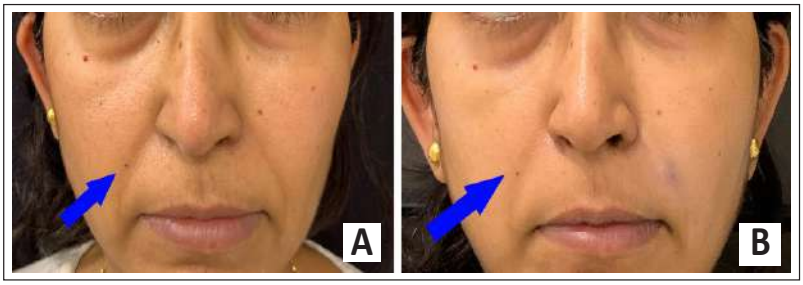

Figure 7– External photograph showing correction of volume of cheek and nasolabial fold with Hyaluronic acid fillers.

A – Flat cheek and deep nasolabial fold before injection. B – Very faint nasolabial fold after correction . Bruise is seen on the nasolabial fold on the left side, which resolves in 1 week .

the cheeks from the lateral side . Results are very gratifying . Complications in the form od sausage appearance , lump ,increased fold and necrosis of the ala nasi may rarely happen .In such a case , it has be hylased immediately. (Figure 7)

6. **Ear lobe –** Deflation of the ear lobe and vertical wrinkles appear on the ear lobe with age . This can be corrected with HA filler injected in the subdermal plane.
7. **Upper and lower lips –** Very helpful for lip augumentation , perioral wrinkles , defining the border and philtrum column .
8. **.Marionette lines –** These are lines on the corner of the lips , which makes the face appear sad .These are caused due to hyperactivity of the Depressor Anguli Oris muscle and the platysma and also due to laxity of the SMAS. Pre treatment with botulinum toxin to relax the DAO muscle is beneficial . The HA filler is injected subcutaneously in retrograde tunnel technique .
9. **Jawline and chin shaping –** Saggy jawline and retruded chin is a sign of ageing . The creation of jowls and pre jowl sulcus adds further to the process. A delicate pointed chin is desired by women , whereas strong , broad chin makes the man look more masculine. HA fillers placed at stragic points with the correct technique , can restore sharp jawline and chin .

My treatment plan consists of 3 steps , as proposed by Dr Maurico de Maio–

1. Foundation – Provide infrastructural support in areas where treatment results would be the most obvious
2. Contouring – Adjust proportions of the upper , mid and lower face by providing a gentle contour and smooth definition .
3. Refinement – Refine details of the facial units e.g shaping of lips , eyes and eyebrows

I assess the full face of the individual and provide the patient with a rejuvenation plan for the full face. I start with foundation points , which involves lifting and supporting the lateral cheek area over the zygomatic arch. Then I concentrate on the pproportion and balance between the upper , middle and lower third of the face. Finally I do the under eye and lips.

In younger individuals with no sagging or age related changes , directly tear trough correction or lip definition can be done , as desired by the patient.

I always keep emergency medicines and hyaluronidase ready, so that in case of inadvertent injection into blood vessel and blanching , the vascular occlusion can be reversed immediately.

Complications of fillers

Most dreaded complication is vascular occlusion. Proper knowledge of anatomy and having hyaluronidase handy is a must. Bluish discolouration can be seen if the injection is very superficial. Nodule formation is rare.

Conclusion

Botulinum toxin and fillers are a good option for patients who want quick results and are not willing to subject themselves to surgical procedures. A through knowledge of the anatomy and interplay between agonist and antagonist muscles of the face, is a must. Being microsurgeons with indepth knowledge of periocular anatomy, ophthalmologists can be one of the best providers of non surgical rejuvenation of periocular area and face.

Financial disclosures – Nil

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Multi-modal imaging in the Pachychoroid spectrum

- Dr. Priyanka Gupta, DNB FVRS, Dr. Sandeep Kumar, MS DNB MNAMS,
Anuj Choudhary, DOT, B.Opt, Dr. Daraius Shroff, MS FRCS
Vitreoretinal and advanced Imaging Services, Shroff Eye Centre, New Delhi

Abstract:

Pachychoroid is a novel term which describes a phenotype characterized by thick choroid, pachyvessels and attenuation of choriocapillaries. It comprises different clinical entities which have common as well as individual features.Entities within the pachychoroid spectrum of disease are growing and emerging along with

the rapid advancements in retinal imaging technology. OCT and OCT angiography have provided us with qualitative and quantitative assessment of choroidal and choriocapillaries changes in this spectrum of diseases.

OCT angiography is particularly useful in looking for active and silent choroidal neovascular membranes. Ultra-wide field imaging has been particularly useful in peripheral choroidal pathologies of this spectrum. We summarize all these modalities and explain their insights into novel findings related to these entities.

Keywords: Pachychoroid, Haller's layer, swept source optical coherence tomography, ICGA, Fundus fluorescein angiography, autofluorescence

Introduction:

Pachychoroid is a relatively new term meaning thickened choroid. The term "pachychoroid was first introduced in 2013 by David Warrow, Quan Hoang and K. Bailey Freund. [1] Initially characterized by phenotype, other features have been added that form the pachychoroid spectrum to play an important pathognomic role in the development of the clinical manifestations. Pachyvessels (dilated Haller layer vessels), attenuated inner choroidal layers (the Sattler layer and choriocapillaris), choroidal hyperpermeability on ICGA, reduced fundus

tessellation in the area of thickening, and club-shaped posterior terminal morphology of pachyvessels are all features of pachychoroid disease; [2] however, eyes do not need to have all of these features to be included in the pachychoroid disease spectrum. The presence of hypertrophy or congested vessels in the choroid (pachyvessels), rather than thickening choroid per se, under a region of decreased or nonexistent choriocapillaris in the posterior pole, appears to be the most distinguishing feature of pachychoroid. Central serous chorioretinopathy (CSCR), pachychoroid pigment epitheliopathy (PPE), pachychoroid neovasculopathy (PNV), polypoidal choroidal vasculopathy (PCV), focal choroidal excavation (FCE), and Peripapillary pachychoroid syndrome (PPS) were originally included in the Pachychoroid Spectrum Disease (PSD). Recently PEHCR has also been suggested to be a part of PSD. [3] In this era of imaging, studies on pachychoroid entities have

grown as a result of the rapid progress of diagnostic technology. Detailed awareness of the most recent multimodal imaging features is required for efficient diagnosis and management of pachychoroid entities since the use of these developing modalities may change the approach to pachychoroid in the future.This review is based on current literature with an emphasis on the clinical and imaging features, the review is divided by covering the individual PSD according to the imaging modality and characterization of the findings in the various clinical entities.

Common characteristics of Pachychoroid diseases :(Table 1)

1. Focal or diffuse thickening of choroid:

There's a wide range of sub-foveal choroidal thickness, with a cutoff value for pachychoroid disorders of 200-390 m^2. Age, sex, axial length, lens status, diabetes, systemic hypertension, and time/diurnal variation of the day all affect the typical sub foveal choroid thickness.Setting a normal threshold for it is therefore challenging, and as a result, numerous investigations have generated a wide range of normative data. [4] The normal sub foveal choroidal thickness in the Indian population is reported to be 299.1± 131.2µm. [5,6,7]

2. Pachyvessels:

They are seen as large hypo reflective lumen located at the level of Haller's layer. Increases in choroidal thickness occur due to dilatation of choroidal vessels in the Haller layer.

3. Attenuation of inner choroid

Involves focal or diffuse attenuation of choriocapillaries and small calibre vessels in the Sattler layer overlying abnormal dilated Haller layer vessel." .[8]

Table 1: Key features of pachychoroid spectrum

1.	Choroidal Thickening
2.	Characteristic presence of Pachyvessels : Dilatation of large vessels in Haller layer
3.	Attenuation of small calibre vessel in Sattler layer
4.	Choroidal Hyper permeability

The following entities are included in the spectrum of pachychoroid disorders:

- **Uncomplicated pachychoroid (UCP)**
- **Pachychoroid pigment epitheliopathy (PPE)**
- **Central serous chorioretinopathy (CSCR)**
- **Pachychoroid neovasculopathy (PNV)**
- **Aneurysmal type 1 neovascularization (AT1N) or polypoidal choroidal vasculopathy (PCV)**
- **Peripapillary pachychoroid syndrome (PPS)**
- **Focal choroidal excavation (FCE)**
- **Peripheral exudative haemorrhagic chorioretinopathy (PEHCR):**

Clinical entities and Imaging features of Pachychoroid spectrum:

1. Pachychoroid pigment epitheliopathy (PPE):

The term PPE was first introduced by Warrow and colleagues. [9] They have been characterised as RPE changes occurring at the posterior pole over areas of choroidal thickening .[9] The age group of patients are typically young and are often seen in fellow eyes of CSCR or PNV and is not visually significant. These cases are sometimes misdiagnosed as RPE epithelitis or age-related macular degeneration .[9,10] Pachychoroid pigment epitheliopathy refers to a precursor or forme fruste of CSCR. The RPE lesions that can be observed in eyes with PPE are: microbreak, RPE thickening, hyperreflective spike of RPE, pigment epithelial detachment (PED) and pachydrusen.

Imaging features: (Fig 1)

The *fundus appearance* in these eyes is typical absence of soft drusen which is often seen in age-related macular degeneration and is characterised by RPE mottling with decreased fundus tessellations. *OCT* will show choroidal thickening with the presence of pachyvessels and focal RPE alterations. No Choroidal neovascular membrane or neurosensory detachment is seen. Interestingly, the outer nuclear layer was seen to be thinner in these eyes as compared to uncomplicated pachychoroid eyes which indicate that photoreceptors and/or RPE degeneration could occur independently in the absence of subretinal fluid. [11] *ICG* shows choroidal hyper permeability with pachyvessels and Autofluoroscence shows mixed granular patterns corresponding to other imaging modalities

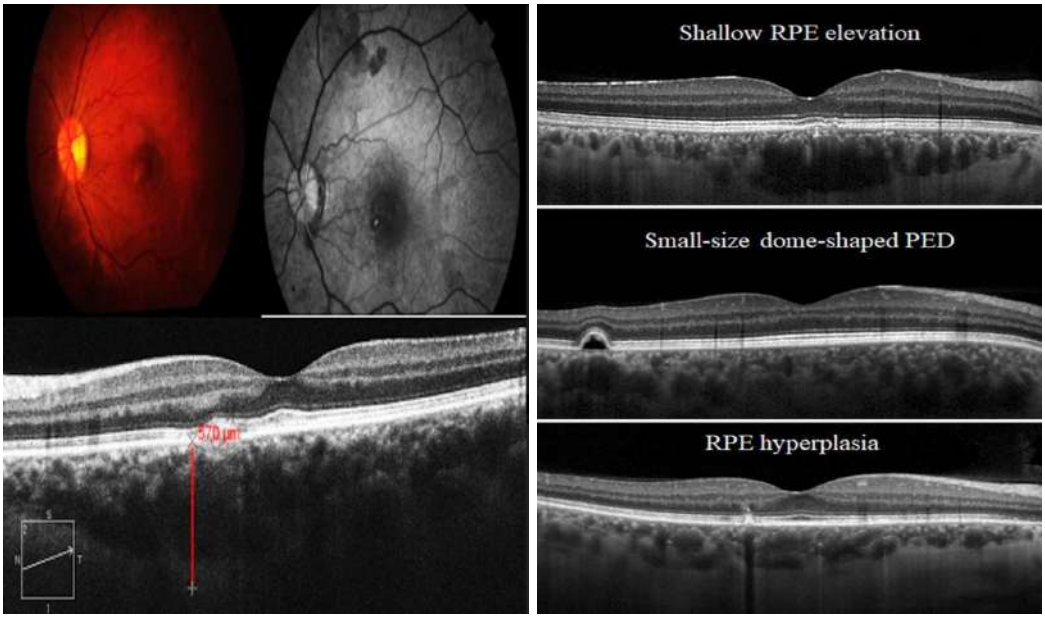


Fig 1: Pachychoroid pigment epitheliopathy (PPE) : multicolour image depicting RPE alterations at macula with corresponding autofluorooscence showing granular pattern . OCT shows focal RPE undulations with presecence of pachyvessels and increased choroidal thickness.

2. Central serous chorioretinopathy (CSCR):

CSCR is characterised by serous PED with neurosensory detachment. Von Graefe first coined the term “central recurrent retinitis” and later on Gass gave the name “central serous choroidopathy” in 1967 . [12,13] The choroidal changes in this entity are mainly focal, multiple and not diffuse.

Imaging features: (Fig 2)

In CSCR the fundus appearance can be of two types depending upon their duration of disease. Acute disease occurs < 3 months and chronic which persists for more than 6 months. In Acute cases, there will be NSD associated with or without PED, which is typically seen as small defined elevated area orange colour present deep to NSD. These cases may sometimes be associated with sub-retinal fibrin. As compared to chronic cases will present as granular RPE mottling with shallow NSD.

Autofluoroscence classical appearance of the presence of vertical gravitational tracts which can be hypo/hyper autofluoroscence & mixed.

FFA shows a typical ink blot pattern or smoke stack pattern in acute cases. These leaks can be single or multiple also. On contrary in chronic cases, FFA will show stippled hyperfluoroscence with staining due to underline window defect.

ICGA in acute cases will show diffuse choroidal hyperpermeability with visible large pachy vessels. In chronic cases, there may be diffuse hypercyanescence in areas of RPE mottling.

OCT will show serous NSD with /without PED. Sometimes they have associated sub-retinal fibrin which is seen as heterogeneous reflectivity within the neurosensory elevation.

Sometimes due to persistence of sub-retinal fluid there may be intraretinal lipid deposition with sub retinal yellowish dots and may lead to elongation of photoreceptor outer segments. [14] Research-based on EDI have shown thickened choroid in these eyes. [15,16] Imamura et al [15], yang et al [17] have found there is an increased thickness in both affected and asymptomatic fellow eyes of patients with CSC. [18] The enface SS-OCT shows presence of pachyvessels which are seen as focal or diffuse choroidal dilatation at both Hallers and sattlers layer. [19]

OCT angiography is used to identify and differentiate non-invasively from other entities particularly the presence of choroidal neovascularization (CNV) secondary to chronic CSC.

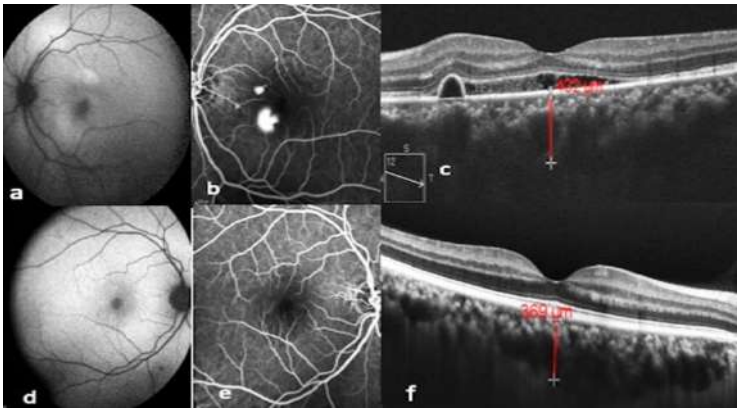
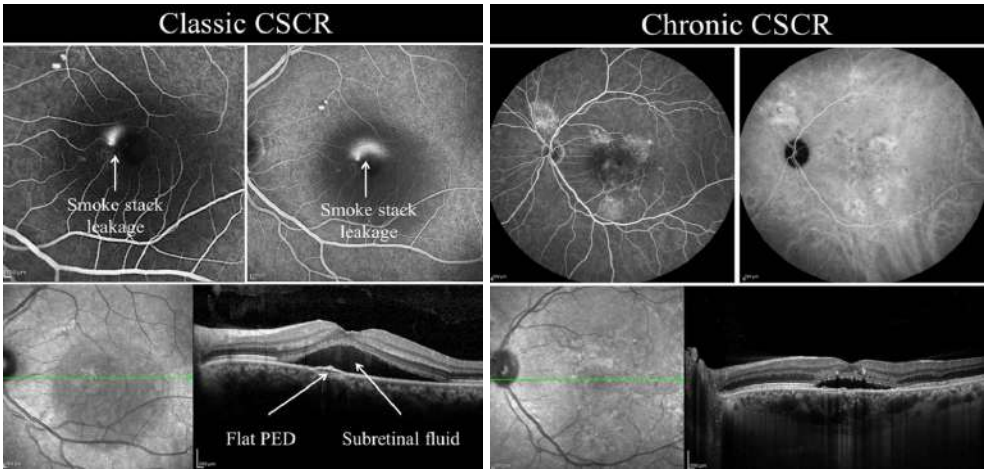


Fig 2: Central serous chorioretinopathy(CSCR): Left eye Autofluoroscence (a) shows hyperfluoroscence at macula with FFA (b) shows smoke stack leakage inferior to fovea. OCT (c) shows neurosensory detachment with adjacent PED with increased choroidal thickness and presence of pachyvessels. Right eye (fellow eye) : Autofluoroscence and FFA (d,e) shows no leakage and OCT (f) shows presence of pachyvessels with increased choroidal thickness.

3. Pachychoroid neovasculopathy (PNV)

Pang and Freund were the first to describe PNV in eyes developing type 1 CNV over background changes of PPE [20] . Pachychoroid Neovasculopathy is usually identified as an incidental finding in patients with a history of chronic CSCR, with or without associated sub-retinal fluid collections.



Miyake et al [21] in their study proposed that PNV with polypoidal lesions should be distinguished from nAMD with polypoidal lesions. As compared to nAMD,PNV was illustrated by a lack of drusen, earlier onset, greater sub foveal CT, higher prevalence of RPE abnormality and choroidal vascular hyperpermeability.

Type-1 CNV was detected in %74-95 of pachychoroid eyes with shallow irregular PEDs using OCTA. Pachychoroid neovasculopathy may appear as active or inactive macular neovascularization. It is thought that 11% of PNVs are inactive lesions. CNV associated with chronic CSCR may be type 1 or type 2. Type 2 CNV in pachychoroid eyes is a distinct condition and a standardized definition has not yet been established.

Imaging features:(Fig 3)

The **fundus appearance** shows a dirty grey membrane with minimal exudation and retinal haemorrhages. CNV is the chief feature of PNV, which may be foveal or extrafoveal in location.

Autofluorescence reveals an abnormal FAF suggestive of RPE changes overlying areas of pachyvessels. Although Chronic CSCR exhibits comparable symptoms, the typical vertical gravitational tracts may not be present. This difference will be helpful in determining whether the SRF is due to the consequence of PNV or CSCR. [20] The presence of neovascularisation can be seen as early hyperfluoroscence with late leakage on FFA and a corresponding late plaque will be seen on ICGA.

OCT will demonstrate the existence of type 1 neovascularization, which manifests as a "double layer sign" covering pachyvessels and appears as a shallow, uneven separation of the RPE from Bruch's membrane known as FIPED. Localized choroidal thickening was alsoobserved in these conditions in contrast to typical nAMD eyes which often have evidence of choroidal thinning .[22,23]

OCTA helps in the diagnosis and confirmation of neovascularization in cases of suspected PNV. Neovascularization can be recognised noninvasively as a tangled network of flow signals between the RPE and Bruch's membrane corresponding to the FIPED seen on structural OCT. In a series of 88 patients with chronic CSC, neovascularization was detected in 35.6% of eyes with shallow irregular PEDs using OCTA. [24] Using OCTA, Carnevali et al [25] described quiescent CNV in 10% of eyes which were diagnosed as PNV.

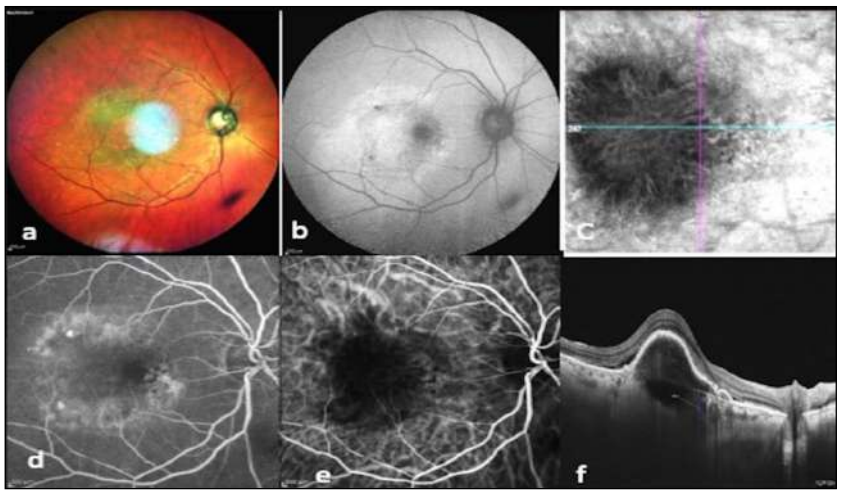
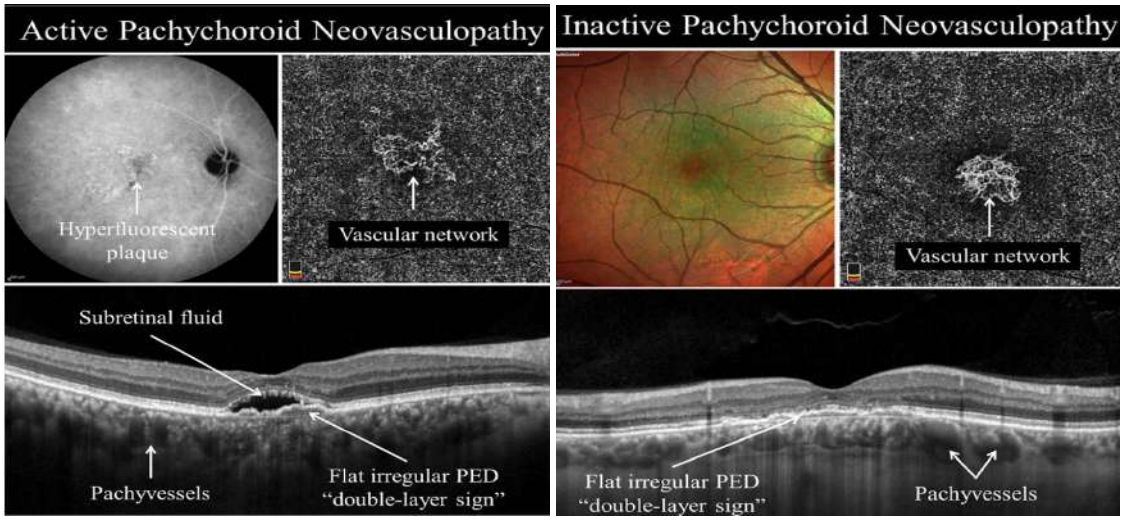


Fig 3: Pachychoroid Neovasculopathy (PNV): Right eye Multicolour image (a) shows RPE alterations at macula with corresponding autofluoroscence (b) shows gravitational mixed autofluoroscence tract. OCTA (c) confirmed the presence of vascular network. FFA &ICG (d,e) shows stippled fluorescence with no definite leakage or hot spot. OCT (f) shows NSD with hyper reflective, fibro vascular PED with increased choroidal thickness and presence of pachyvessels.



4. Polypoidal choroidal vasculopathy/ Aneurysmal Type 1 Novascularization

Yanuzzi et al. first identified polypoidal choroidal vasculopathy [17] (PCV), which was thought to be a subtype of nAMD. Polypoidal lesions, which are identified as dilations of branching vascular network (BVN) terminals, are the hallmark of PCV. Eyes with PCV have a greater mean sub foveal choroidal thickness (SFCT). Despite being the gold standard [26] for diagnosing PCV, ICGA is an invasive imaging procedure that should not be used on patients who have a history of iodine-based dye allergies. Therefore, using non-invasive imaging techniques to diagnose PCV may be helpful in clinical practice.

Imaging features (Fig 4)

PCV is characterised by protruding orange-red nodular lesions [27] on colour photos.They are typically found at the posterior pole, in the macular or peripapillary region which according to the Japanese Study Group of Polypoidal Choroidal Vasculopathy was a significant diagnostic criterion. [27] Serous exudation and haemorrhage are frequently present with nodular lesions.Polyp lesions are mostly present at the margin and inside the serosanguinous PED,appearing as a "notch sign on OCT. [28] On AF the polyp either appears as a hyperfluorescent ring or even granular hypo fluorescence. As the BVN is located in Bruch's membrane PCV

appears as occult or minimal classic AMD on FFA. [28,29] The RPE in FA makes it difficult to see the BVN beneath it unless the RPE above it has atrophy or the fundus is less pigmented,that's why it appears with classic hyperfluoroscence in cases of atrophy of overlying RPE or subretinal fibrin deposition or presence of type 2 CNV. [30] FFA has limitations in cases with serosanguinous deposits due to blocked fluorescence by heme or exudates. In such cases,ICGA has proved to be diagnostics in the visualisation of polyps. Within the first six minutes after the dye injection, PCV presents with one or more focal areas of hyperfluoroscence originating from the choroidal circulation, with or without an accompanying BVN. The PCV nodules and aneurysm are visualised as ICGA hyper fluorescence on the edge of BVN [31] .Active polyps have a hypo fluorescent halo that surrounds them, indicating that there is fluid around the polyp. Based on ICGA, PCV into two categories [32] : Type 1, there are many network vessels and both feeder and draining vessels are visible on the ICGA; in Type 2,

there are few network vessels and neither feeder nor draining vessels are visualised.ON SD-OCT the PCV has the following signs [33] .1) A sharp peak-like or thumb-like PED.2) the double-layered sign.3) Underneath the PEDs, a region of hypo reflectivity is surrounded by a moderately hyperreflective ring.4). "V"-shaped depression between two PEDs or at the margin of a large PED. 5) Multiple PEDs. Based on EDI, PCV was subclassified into two subtypes [34] : Typical PCV with thick choroid and PCV without thick choroid using choroidal vascular characteristics (polypoidal CNV). SS-OCTA has been a new addition to our armamentarium in diagnosing PCV, esp. in cases who ae allergic to ICGA dye. It has been observed that BVNs are better delineated on OCTA than on ICGA, but do not show the polyps as clearly as ICGA. Various authors have

described polyps on OCTA as either a hypo flow round structure at the level of the choriocapillaris or a hyper flow round structure surrounded by a hypo flow halo. Artefacts and auto-segmentation are the limitations of OCTA that cautions interpretation of the images. Recent studies have shown a wide range in the detection rate of polyps on OCTA compared to ICGA, from 45% to 92% detected .[35]

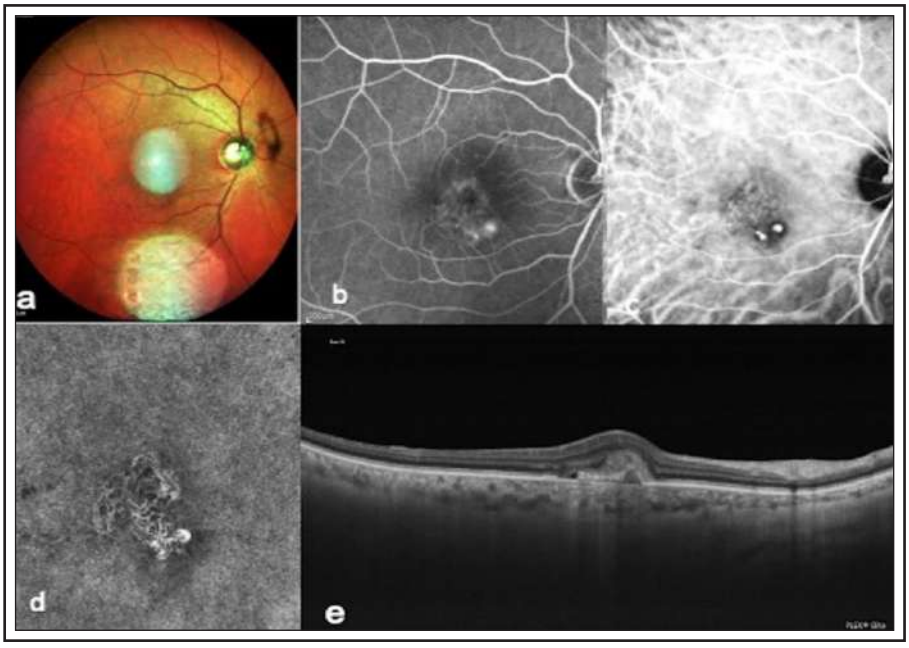
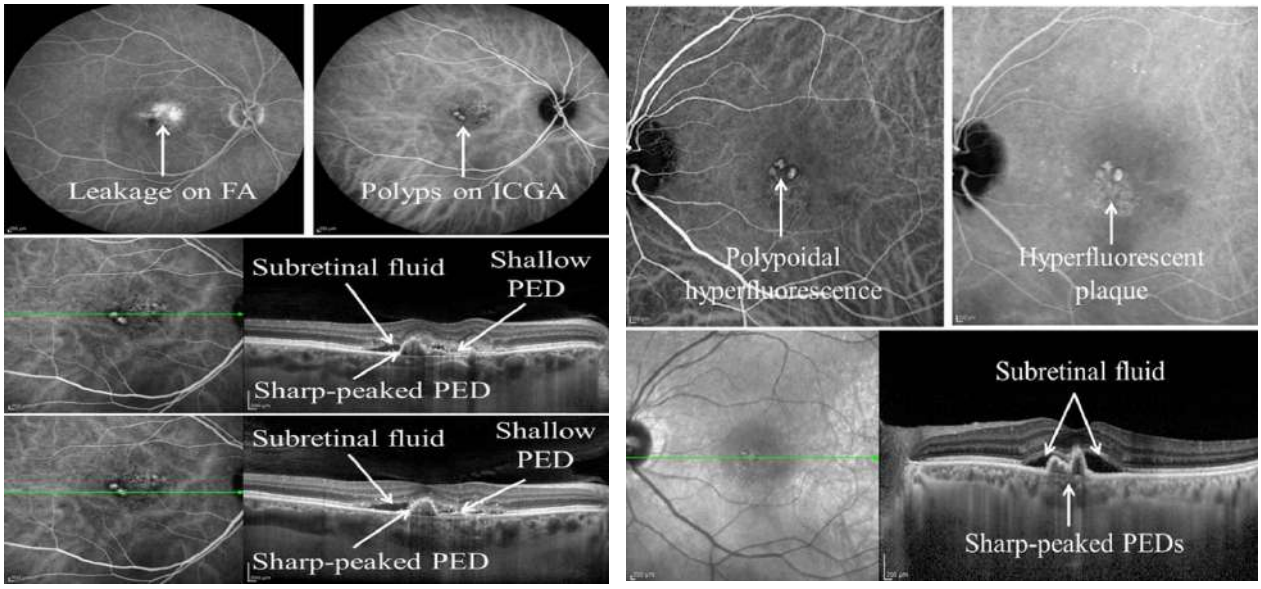


Fig 4: Polypoidal choroidal vasculopthy (PCV): Right eye Multicolour image (a) shows sub retinal heme at macula. FFA & ICG (b,c) shows leakage and presence of polyps at inferior to fovea. OCTA (d) at choriocapillaries slab shows presence of branching vascular network with corresponding OCT (e) shows NSD with double layer sign with presence of pachyvessels and increased choroidal thickness underneath.



5. Peripheral exudative haemorrhagic chorioretinopathy (PEHCR):

First reported in 1961, the spectrum of peripheral PEDs and haemorrhage was coined the name 'PEHCR' by Annesley in 1980. [36] Given the similarities between PEHCR and exudative age-related macular degeneration, several authors have proposed that PEHCR may result from a choroidal neovascular network .[37] While others have other authors have suggested that PEHCR could be more likely to share a common pathophysiological origin with polypoidal choroidal vasculopathy. [38] Recently Shroff et al [3] proposed to include PEHCR in the

pachychoroid spectrum of disease entities, based on their findings that the mean temporal Choroidal Thickness(CT) is 60 mm more than the mean SFCT in PEHCR and the area of maximum CT coincides with the site of the lesion.

Imaging features (Fig 5)

Fundus appearance

Lesions are most frequently discovered in the temporal quadrant, and between the equator and the ora serrata, in more than 75% of cases. [39] Nasal lesions are occasionally present alongside temporal lesions, either as an extension of a large temporal lesion or as separate lesions, and are frequently accompanied by bilateral involvement haemorrhagic PED, lipid exudation, subretinal fibrosis or haemorrhage, or even vitreous haemorrhage.

On FFA PEHCR haemorrhagic lesions show a significant masking effect, sometimes associated with the hyperfluoroscence of associated CNV. The most common FA findings are the blockage of choroidal fluorescence related to haemorrhage (subretinal/sub RPE) and window defect from peripheral atrophic RPE changes. [40] Other findings include diffuse peripheral hyper- or hypo fluorescence that correlates to RPE atrophy or hyperplasia.20 of the 56 PEHCR eyes in Mantels 2009 series underwent ICG-A and 6 (30%) of them had pathologic choroidal vascular networks that resembled those observed in polypoidal choroidal vasculopathy (none of them had associated FA findings of neovascularization). [40]

Wide-field ICGA allowed us to identify delayed filling

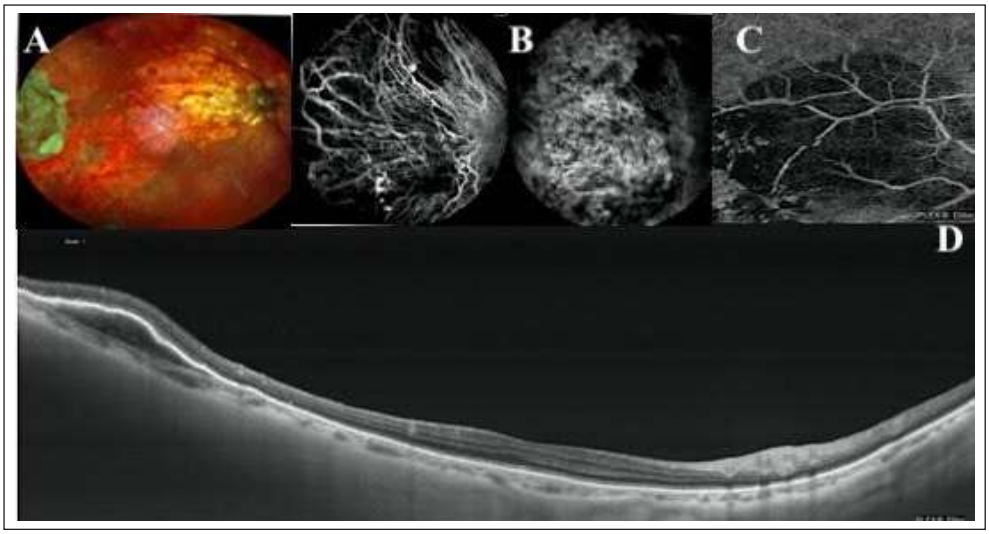


Fig 5: Peripheral exudative haemorrhagic chorioretinopathy (PEHCR): Multicolour image shows temporal subretinal lesion with exudation. FFA&ICG shows peripheral polyp-like choroidal telangiectasia and abnormal choroidal vascular networks. OCTA shows high flow network correspondingly. OCT shows a temporal increase in choroidal thickness with the presence of pachyvessels underneath with PED.

of the choriocapillaries in peripheral areas of pigmentary changes and atrophy in the periphery, denser choroidal veins,peripheral polyp-like choroidal telangiectasis and abnormal choroidal vascular networks.Recently, Widefield SS-OCTA has proved to be very helpful in avoiding misdiagnosis of PEHCR and formulating a treatment plan. The polyps are seen as a cluster of dilated vascular

networks on the en face SS-OCTA and each of these networks showed a corresponding high flow signal on SS-OCTA. Gupta et al 41 were also able to identify a BVN below the cluster of polyps on en face SS-OCTA. The PCV lesion complex on SS-OCTA correlated well with the ICGA.

6. Peripapillary Pachychoroid syndrome (PPS):

Peripapillary pachychoroid syndrome is a part of pachychoroid spectrum disorder which is

first described by Phasukkijwatana et al. [42] It is characterised by pachychoroid features seen in the peripapillary area and nasal macula rather than the fovea. The most common differential diagnosis of this entity is uveal effusion syndrome since it is associated with hyperopia, crowded disc and serous retinal detachment at the posterior pole. The differentiating feature is no choroidal detachment is seen in this entity

Imaging features. (Fig 6)

The clinical features include intraretinal and/or subretinal fluid in the peripapillary area and optic nerve head oedema.

Autofluoroscence shows mottled hypo fluorescence and gravitational tracks in the peripapillary area.

FFA shows window defects in the corresponding areas without focal leakages. Mild late disc leakage may be seen in the majority of the cases. ICGA shows Choroidal vascular hyperpermeability and presence of pachyvessels. OCT shows intraretinal fluid and NSD in the Peripapillary area with thickened choroid and the presence of pachyvessels with choriocapillaries attenuation. The thickened choroid was especially noted in the nasal versus temporal macula when compared to other typical pachychoroid spectrum disorders.[43]

7. Focal choroidal excavation (FCE):

Jampol et al in 2006 [44] with time domain OCT mentioned FCE as an unusual concavity in the choroid occurring without posterior staphyloma or scleral ectasia. Margolis et al in 2011 45 coined the term “Focal Choroidal Excavation”. Chung and co-workers found increased choroidal thickness and presence of pachyvessels in OCT and choroidal hyperpermeability in ICGA in eyes with FCE. They suggested FCE as a distinct entity in PSD. The refractive error of many reported eyes with FCE was myopic; however, reports of FCE in emmetropic patients are not infrequent. [46]

Imaging features: (Fig 7)

On clinical examination, there may be no visible funduscopic abnormalities that appear to correlate with the FCE detected on structural OCT. Colour fundus photographs of both eyes show subtle alteration of the RPE between enlarged choroidal vessels or show scattered pigmentary disturbances including the fovea. Sometimes the non-conforming variant appears as patchy areas of macular atrophy with a granular appearance or an accumulation of yellowish vitelliform-like material. Both hyper autofluorescence and hypo autofluorescence has been found in the fundus on autofluorescence, and they seem to correspond to RPE alterations that may happen with FCE. Based on the results of SD-OCT, FCE is categorized into two patterns [45] :

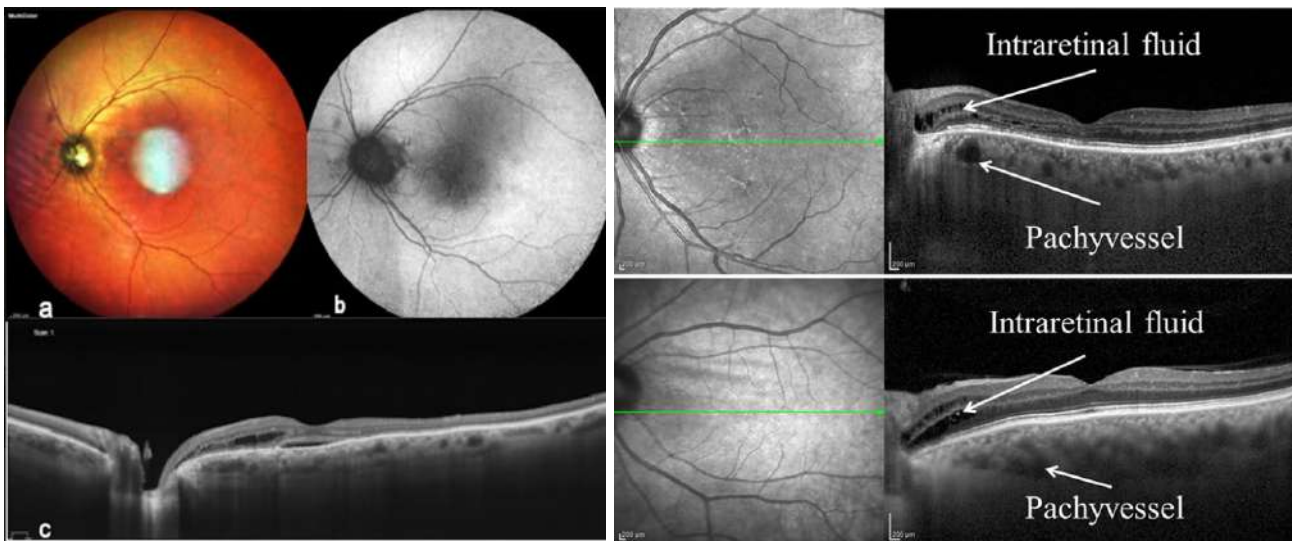


Fig 6: Peripapillary Pachychoroid syndrome (PPS): Left eye. Multicolur shows RPE alterations nasal to fovea with corresponding autofluoroscence showing same . OCT shows NSD with few intraretinal cystic spaces in nasal quadrant with underline increased choroidal thickness and presence of pachyvessels.

Conforming FCE -Those lacking a gap between the photoreceptors and RPE.Nonconforming FCE- The photoreceptor tips in the affected area were separated from the underlying RPE. Based on the OCT appearance, Shinojima et al [46] . defined three morphologic forms: cone-shaped, bowl-shaped, or mixed type. Atrophic changes were least noted in cone form.

There have been several accounts of FCE occurring in conjunction with other macular findings, such as central serous chorioretinopathy (CSC), choroidal neovascularization (CNV),nonneovascular age-related macular degeneration, and vitelliform macular disease [47,48,49] .Ischemia and RPE changes could precipitate CNV in some eyes with FCE as suggested by ICGA findings including choroidal filling defects, choroidal venous dilation, and focal or punctate hyperfluoroscence.

Depending on the degree of the RPE changes, isolated lesions of FCE on FFA exhibit various degrees of hyperfluoroscence and hypo fluorescence. In the mid- or late- phase FA, hyperfluoroscence owing to transmission faults linked to RPE attenuation without leakage may be observed.

EDI shows increased choroidal thickness with dilated choroidal vessels immediately surrounding or outside the area of FCE; SS-OCTA frequently detects the presence of pachyvessels, which are spatially correlated within the region of choroidal thickening linked to FCE. [50] In cases of FCE with type 1 or 2 or mixed ones, SS-OCTA may be helpful in the early detection of neovascular membranes or networks, that might be missed on SD-OCT.

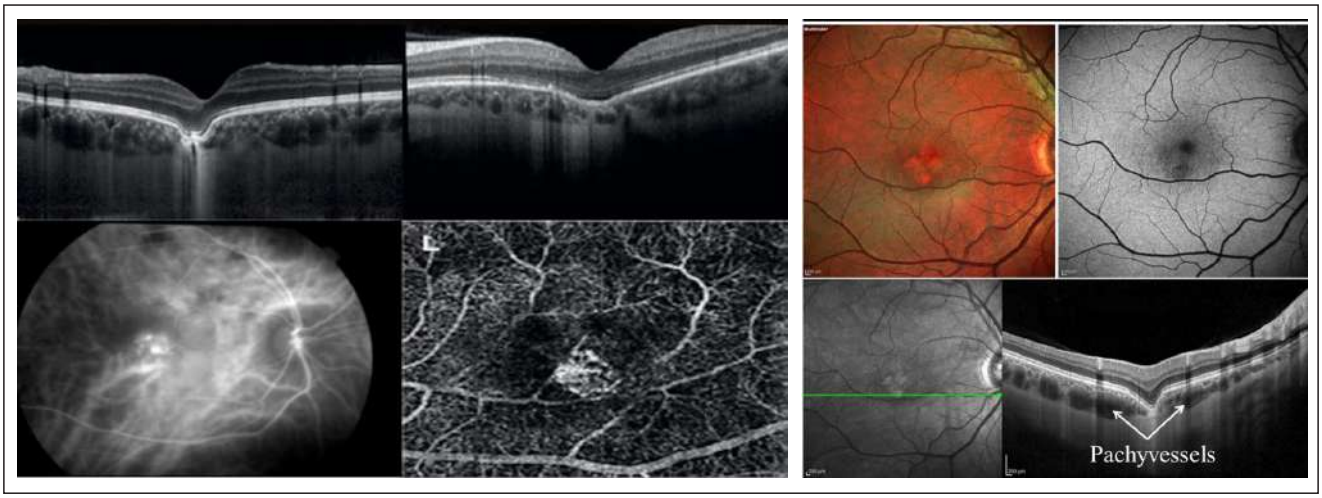


Fig 7: Focal choroidal excavation (FCE): OCT shows Cone shaped and bowl shaped excavation with surrounding presence of pachyvessels and increased choroidal thickness. ICGA shows presence of hypercyanescence with pachyvessels seen. OCTA shows presence of vascular network.

Conclusion

Advancements in imaging technology have helped us garner a proper understanding of pathological process implicated in pachychoroid diseases. MMI helps in enhanced disease diagnosis and therapy monitoring. MMI can also help in tailoring the treatment protocol according to the individualized needs of the patient.

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Pediatric Corneal Transplants: Perioperative, Operative, and Postoperative Management

- Dr. Vinay Sukumara Pillai[1]

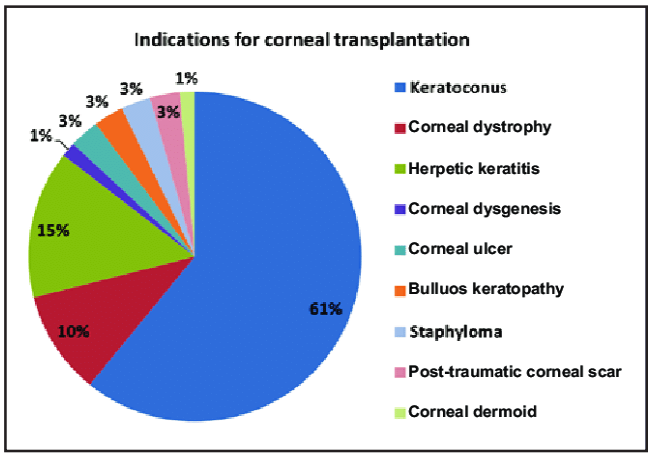
[1]Head of Cornea & Refractive Surgery at Giridhar Eye Institute, Ernakulam, Kerala, India

Introduction

Corneal transplantation or penetrating keratoplasty (PKP) involves a partial or full-thickness replacement of corneal tissue with donor cornea and has advanced tremendously since the surgery was developed in the 1970s.[1] Although corneal transplantation is a surgery frequently performed in adults, the indications, intraoperative complications, and postoperative management difficulties associated with pediatric corneal transplant make it a relatively uncommon surgical procedure, accounting for ~5% of all corneal transplants worldwide.[2] The etiologies and indications for pediatric corneal transplants vary widely and differ from adults (Table 1).[6,7] In the developed world, the most common indications for pediatric keratoplasty include congenital corneal opacities, anterior segment dysgenesis (most commonly Peters' anomaly), and keratoconus.[2,3,8–12] In developing nations, corneal scarring from acquired causes such as infectious keratitis and corneal trauma comprise the majority of the cases.[3,13–15]

Pediatric Keratoplasty[2–5]	Adult Keratoplasty[6]
Congenital nontraumatic*	Keratoconus*
CHED	PBK*
Congenital glaucoma	Fuchs dystrophy*
Peters' anomaly	Other corneal dystrophy
Sclerocornea	Infectious keratitis
Dermoid	Corneal scar
Microphthalmia	Failed graft
Birth trauma	
Metabolic disease	
Aniridia	
Acquired traumatic corneal opacity	
Acquired nontraumatic corneal opacity	
Keratoconus*	
Infectious keratitis	
Noninfectious keratitis	
Postinfectious corneal scars	
Keratomalacia	

*Most common indications.
CHED indicates congenital hereditary endothelial dystrophy; PBK, pseudophakic bullous keratopathy.



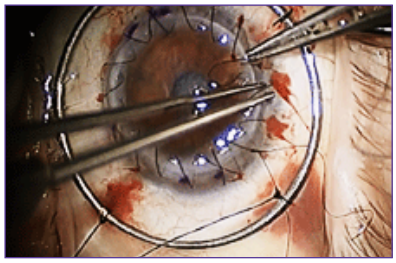
The relative paucity of pediatric corneal transplantation is due to a combination of factors including the surgical complexity of the procedure, differences in pediatric versus adult anatomy, barriers in postoperative management, and high risk of amblyopia development in the pediatric population. The corneal transplant procedure is more technically challenging due to the smaller size of the globe, reduced corneal and scleral rigidity, presence of associated anterior segment abnormalities, and increased posterior pressure from a dense vitreous leading to anterior displacement of the lens-iris diaphragm.[8,13–16] Typically, additional steps need to be performed preoperatively or intraoperatively to lower the posterior pressure and allow the donor cornea to be sutured into position, including intravenous mannitol administration or anchoring sutures before removing the host cornea. The high rate of iris prolapse intraoperatively makes the surgical technique also very challenging.

Postoperatively, children develop a more robust inflammatory response which places them at a higher risk for secondary glaucoma, cataract, and graft rejection, and failure.[4,11,15–17] Some surgeons advocate for intraoperative steroid administration either intravenously, intracamerally, or subconjunctivally to better control postoperative inflammation. Children are also prone to suture-related complications including suture breaking, loosening, or suture-related microbial keratitis necessitating frequent examinations (with or without general anesthesia) with the high probability of additional surgical interventions. Another consideration specific to the pediatric population is visual rehabilitation and treatment of amblyopia after a successful anatomic outcome.[2,8,18,19] Irrespective of which suture technique is used to secure the corneal graft, there is often a large amount of astigmatism which persists in the visual axis. The astigmatism needs to be corrected by prescription glasses, rigid gas-permeable lens, or

occasionally standard toric contact lenses. This refractive amblyopia risk, in addition to the preoperative deprivational and/or refractive amblyopia, can lead to postoperative suboptimal visual potential. In general, outcomes of pediatric corneal transplants are less than favorable compared with adults because of the aforementioned challenges.[1,4,17,20] Prognosis and graft survival depend on several factors, including patient age and underlying etiology.[5,21] Nonetheless, with advancement in surgical procedures and a better understanding of preoperative, intraoperative, and postoperative management, pediatric keratoplasty outcomes and graft survival have improved in the recent years giving select patients potential for visual improvement (Table 1).[5,10]

Types of Pediatric Corneal Transplants

Penetrating Keratoplasty (PKP) Full-thickness PKP has traditionally been the surgical technique for children requiring corneal transplantation due to the ability to completely excise all corneal pathology in one procedure.[20] The surgical technique for PKP involves trephining the diseased host cornea, filling the anterior chamber with a viscoelastic agent, then excising the host corneal button. The donor cornea button is trephined with typically a 0.5 to 1.0 mm oversized trephine and sutured to the host corneal rim with either interrupted sutures, a single running suture, or a combination of both.[14] A variation on PKP is the mushroom keratoplasty. This 2-part graft procedure involves transplanting a smaller central area of the endothelium and deep stroma with a larger anterior stromal lamella.[22] The smaller penetrating keratoplasty is thought to confer a graft survival advantage by preserving the host endothelium, combined with the refractive advantage of a large anterior lamellar keratoplasty. Furthermore, there is thought to be a stronger wound profile, allowing for earlier removal of sutures and decreased risk of dehiscence from minor trauma.



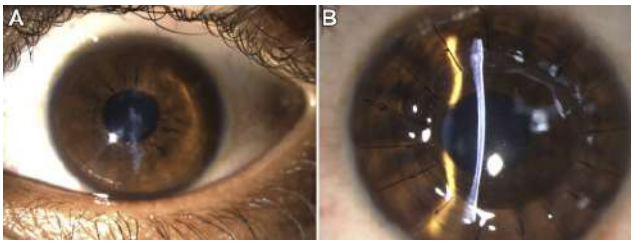
Endothelial Keratoplasty (EK) In more recent years, EK has surpassed PKP as the predominant treatment method for endothelial dysfunction in adults.[23] While PKP is far more common than EK for pediatric patients, EK procedures have steadily increased over the years but still lags behind the adoption of PKP due to surgical complexity in a pediatric eye.[3,23] EK surgery involves removing the dysfunctional endothelium and Descemet membrane and replacing it with a healthy donor lamellar graft.[11] The advantage of EK over standard penetrating keratoplasty is a faster procedure time, less postoperative astigmatism, decreased risk of suture-related complications, and quicker visual rehabilitation with decreased risk of amblyopia.[11] The EK surgical technique is generally the same for children and adults; however, EK in children presents with additional challenges.

Structurally, there is increased positive posterior vitreous pressure along with a relatively more anterior lens-iris diaphragm causing the anterior chamber to be shallower and more prone to collapse, with limited space for tissue manipulation.[11,24] Visualization may be poor due to pathology of the anterior cornea, especially with any corneal scarring or edema, especially with a smaller horizontal corneal diameter in the pediatric eye,[23,24] and there may be relatively stronger adhesion of Descemet membrane to the posterior stroma.[11] Furthermore, stripping of the Descemet membrane could cause inadvertent trauma to the lens and/or posterior stromal fibers due to the shallow anterior chamber.[24] For these reasons, some surgeons[24] have performed non–Descemet-stripping EK with comparable results to Descemet-stripping EK.

Deep Anterior Lamellar Keratoplasty (DALK) For patients with a healthy endothelium, DALK has become the surgery of choice due to the lower risk of endothelial rejection.[11,25] Stromal rejection is thought to be relatively uncommon with a milder pathology in DALK patients.[11] Nonetheless, initial intensive steroid treatment with regular examinations is still warranted to prevent and/or treat any stromal rejection episode.[25] DALK surgery involves removing the affected epithelium and stroma while leaving the host endothelium intact.[25] Trephination is performed, followed by careful manual dissection to dissect the deep stroma off the Descemet membrane without penetration. Alternatively, a big bubble approach[26] may be done to separate the stroma from the Descemet membrane which involves injecting air in the pre-Descemet plane. The donor button is trephined larger25 (0.25 mm) than the host trephine, and the Descemet membrane is removed. Finally, the donor button is sutured onto the host bed.

DALK has been performed in pediatric patients with keratoconus,[27] mucopolysaccharidoses,[25] and nonherpetic or postherpetic scarring.[28] Though DALK can be technically difficult resulting in longer operative times, the benefits are numerous: risk of endothelial rejection is reduced, steroids and sutures can be discontinued earlier, and host endothelial cell layer is preserved.[27,28] Complications include Descemet membrane detachment, double anterior chamber, epithelial/stromal rejection, graft dehiscence, unpredictable and unstable refraction, high astigmatism, and high myopia.[29] Outcomes vary based on relevant factors such as underlying pathology, age, and surgical technique. A review by Sharma and colleagues reported DALK outcomes from 16 published case reports and case series. Overall, graft clarity was achieved in about 85% (132/156) of eyes.[29] The largest case series to date by Elbaz and colleagues reported clear grafts in 96% (48/50) of eyes at last follow-up, with a mean follow-up time of 36.5 months. Furthermore, they reported an 8.3% loss in endothelial cell density between the DALK eyes and normal

fellow eyes (23 eyes), with a mean follow-up time of 42.7 months.[30] Among the cohort, there were failed grafts in 9.8% (5/51) of eyes and stromal rejection episodes in 9.8% (5/51) of eyes.



Keratoprosthesis

A keratoprosthesis is an artificial cornea that was historically used as a surgical procedure of last resort in patients who were not candidates for a penetrating keratoplasty procedure.[31] The most commonly used keratoprosthesis is the Boston KPro device from Massachusetts Eye and Ear Infirmary (Boston, MA).[32] The KPro procedure involves trephining a button from a donor cornea with a central opening which is inserted between a front plate and fenestrated back plate. The assembled device is inserted into the recipient bed after surgical excision of the diseased host cornea.[31] In phakic patients, lensectomy and anterior vitrectomy are performed concurrently. In aphakic patients, anterior vitrectomy is performed. Some patients may require subtotal iridectomy to allow KPro insertion.[33]

Aquavella and colleagues published the largest pediatric Kpo case series to date in 2007 with 21 pediatric keratoprosthesis procedures. There was no documented dislocation or extrusion, surface infection, or endophthalmitis. Visual outcomes were reasonable, however, follow-up was limited with a mean of 10 months. The potential benefits of keratoprosthesis are numerous: eyes are uninflamed and quiet after the procedure, facilitating examinations without the need of examination under anesthesia.[31] Risk of allograft rejection is significantly decreased, and wound-related astigmatism is minimized. All these benefits can confer a measurable advantage when treating amblyopia in the pediatric population.[31] However, when analyzing long-term data in Kpro devices, there is a paucity of published literature.[34] In 2018, Fung et al[33] published a case series of 11 Kpro implantations with a median follow-up of 26.7 months; these patients faced considerable complications with a high rate of worsening visual outcomes and extruded devices. At the last follow-up, vision in 55% of eyes was worse than the preoperative level; 45% of eyes had lost light perception, and 18% of eyes were phthisical. Complications included: formation of retroprosthetic membranes (82%), sterile corneal melt (45%), retinal detachment (45%), infectious keratitis (27%) which led to endophthalmitis, and exacerbation of preexisting glaucoma in 3 eyes. At the final follow-up, there was a retention rate of only 36%. The authors concluded that they would not recommend Kpro use in the pediatric population; in fact, the 3 centers that participated in the study have stopped offering the Kpro as a treatment option.

Perioperative Considerations

Timing of Surgery

There is no consensus on the optimal timing of pediatric corneal transplantation and is typically dependent on the etiology of corneal opacity.[3,14] Zhu and colleagues reported that 100% of respondents to their survey would perform corneal transplantation before 1 year of age in patients with bilateral congenital corneal opacities, with 41.9% stating that transplantation should occur between 1 and 3 months of age. For patients with monocular corneal opacities, 71.0% of respondents would perform corneal transplantation younger than 1 year of age. Overall, 35.5% reported that transplantation should occur between 1 and 3 months of age; however, 12.9% of participants reported that they would never transplant a patient with a monocular corneal opacity.

For surgeons considering bilateral corneal transplants, the optimal timing and interval between eyes is still up for debate.[14] Shorter time intervals between the first and second corneal transplantation have been recommended to minimize the progression of deprivational amblyopia by balancing visual input from both eyes.[14] However, when the first eye provides sufficient vision, delaying a second transplant may be considered for pediatric patients at high risk for graft failure.[32] The potential risk of deprivational amblyopia development has to be weighed against the risk of corneal graft failure, and there is no general consensus on how to approach these patients. Lowe et al[2] reported that children younger than 5 years old faced worse long-term graft outcomes compared with older children (5 to 12 y of age) with 40% and 70% graft survival at 16 years, respectively. This higher rate of graft failure may be explained by concurrent congenital and developmental disorders with comorbidities that affect graft outcomes.

Donor Characteristics

When deciding on suitable donor tissue for a pediatric corneal transplant, there are many factors to consider. While many surgeons prefer younger donor tissue,[19] the available evidence suggests that donor characteristics have minimal to no influence on graft survival.[1] Factors such as donor age, time from donor death to surgery, time from donor death to enucleation, and time from donor death to placing the donor cornea in McCarey-Kaufman medium, have been studied without any factor reaching statistical significance.[8] Some corneal surgeons prefer tissue from donors older than 4 years of age to prevent low corneal rigidity and accompanying ectasia which makes the surgery even more technically challenging which may occur in tissues from donors less than 2 years of age.[20]

Operative Management

Anesthesia -As with the majority of pediatric

ophthalmology procedures, general endotracheal anesthesia is recommended for patient comfort and safety. Preoperative or intraoperative administration of intravenous mannitol can be considered to decompress the posterior pressure induced by the dense vitreous but should be cleared by anesthesia first to ensure patient safety. In addition, hyperventilating the patient is an intraoperative maneuver that may be performed by the anesthesiologist to help reduce intraocular pressure (IOP) upon surgeons' request.[4] Extraocular muscle contraction should be avoided during surgery as the eye is "open-sky" for part of the surgical procedure,[11,20] therefore, general anesthesia with a nondepolarizing muscle relaxant is recommended.[11,20] The patient should be deep enough to prevent any palpebral-oculogyric reflex (Bell's phenomenon), and the eye should be orthotropic for the majority of the procedure to ensure no additional pressure is needed to counteract any of the extraocular muscles.

Graft Sizing

Grafts are often typically oversized between 0.5 to 1.0 mm larger than the donor trephine[11,20] for most cases of pediatric corneal transplantation to compensate for the relatively flat keratometry values and generally floppy corneal tissue. The appropriate oversizing allows for adequate anterior chamber depth to avoid compression of the trabecular meshwork angle.[20] In older patients with keratoconus, some surgeons prefer to match the donor and host trephine size exactly to flatten the donor cornea and decrease the overall patient's keratometry values.

Medications

Preoperatively, the surgeon can consider the administration of miotic drops (ie, pilocarpine 1%) and/or antibiotic drops.[20] As previously mentioned, posterior vitreous pressure should be reduced to avoid intraoperative iris prolapse, spontaneous lens expulsion, or suprachoroidal hemorrhage after the host corneal button has been excised.[20] The reduction of vitreous pressure can be achieved with intravenous mannitol 0.5 to 1.5 g/kg administration, preoperative ocular massage, and/or intraoperative hyperventilation.[11,14,20]

At the end of the surgery, subconjunctival antibiotics may be administered for antibacterial prophylaxis,[11] and surgeons may opt to administer subconjunctival or topical steroids.11 Furthermore, heparin solution and sodium hyaluronate have been used to help avoid the formation of peripheral anterior synechiae.[11] Stabilization of the Globe Pediatric globes exhibit low scleral rigidity with increased scleral elasticity leading to a higher risk of ocular collapse without appropriate intraoperative support.[11,20] To support the globe, a Flieringa ring can be fixed to the episclera using interrupted sutures.[20,35] Care should be taken to avoid inadvertent needle perforation of the thin pediatric sclera.[11] Furthermore, the interrupted fixation sutures should be equally spaced to avoid irregularity of the graft-recipient bed resulting in postoperative astigmatism.[11]

Other Surgical Modifications

Suture techniques should be optimized for pediatric patient. For rapid placement of the donor tissue onto the host bed, preplaced bridging mattress sutures can be prepared in an interrupted radial fashion (Chan).[20] Two horizontal mattress sutures, in the vertical and horizontal meridian, are placed over the recipient cornea, forming a net. The sutures are draped to the side while the dissection of the recipient button is completed. Once the donor button is placed, the mattress sutures are drawn snug and tied down, recreating a closed chamber. Permanent sutures can then be placed in a more stable setting, and the mattress sutures are removed from underneath the donor tissue.[36] In 2013, Chen et al[37] described a novel approach to PKP inspired by DALK, which involved maintaining the anterior chamber to avoid the pitfalls during an open-sky technique. First, the host cornea was trephined with ~80% thickness of the anterior lamellar stroma removed. Four points are then punctured at the [3, 6, 9], and 12 o'clock positions, and a viscoelastic agent is used to coat the anterior corneal surface. The donor graft is then placed on the stromal bed that was coated with viscoelastic material and sutured at the 4 puncture sites. Sequentially, each quadrant of the residual stromal bed is excised, and the donor graft is sequentially sutured in place. Before the last quadrant is placed, the stromal bed was drawn out of the anterior chamber.

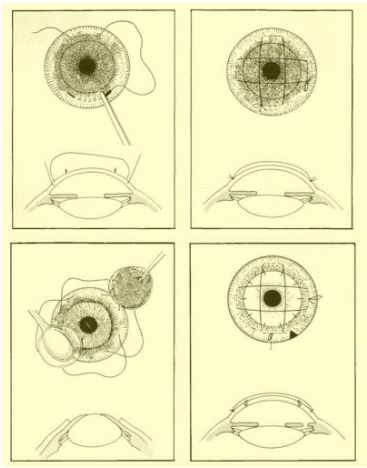


Figure-Mattress bridging sutures for temporary stabilization of donor graft.

Arslan and colleagues described a similar technique that was performed on 72 pediatric eyes and 44 adult eyes. Their technique involved incising and resuturing the recipient button at each 2 o'clock hour segment. The donor button was then placed and sutured to the recipient corneal rim with interrupted sutures, leaving a 2 o'clock hour segment unsutured. The sutures between the recipient button and rim were then cut, the recipient button was removed, and the final suture between the donor button and the recipient rim was placed.[38] They reported no complications related to the open-sky technique and had no significant endothelial cell loss—24% at 12 months, which was comparable to previous penetrating keratoplasty rates.[39]

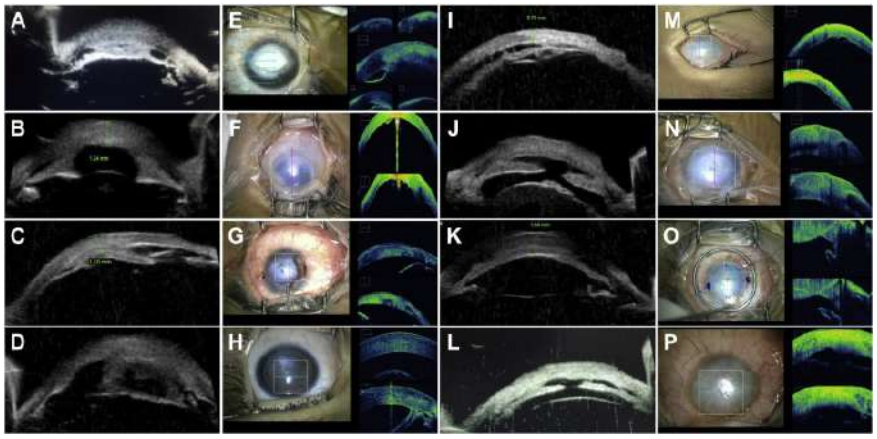
Combined Procedures

Combined procedures have been welldocumented

to be associated with worse corneal graft survival in combination with PKP.[8,9,12,14,15,40] This is in part due to preexisting comorbid conditions in the eyes that necessitate and undergo multiple procedures that affect graft survival.[9] Regardless, most surgeons recommend against combined procedures due to poor outcomes.[15] Combining PKP with procedures such as cataract extraction, vitrectomy, membrane peeling for patients with retinopathy of prematurity[15] and/or glaucoma valve implantation [41] have been associated with poor outcomes. Dana and colleagues reported an odds ratio of 6.42 higher risk of graft failure in patients that concurrently undergo vitrectomy and lensectomy.

Intraoperative OCT-

Anterior segment imaging with i-OCT immediately before keratoplasty improves the surgical planning of children with corneal opacities. In addition, the use of i-OCT refines intraoperative steps, thereby optimizing the postoperative outcome of pediatric keratoplasty.



Postoperative Management

Medications -Frequent topical steroid drops are routinely utilized postoperatively to reduce the risk of graft rejection which occurs more rapidly and frequently in pediatric patients. Although no standard postoperative regimen has been established, typically, high dose topical steroid drops are initiated in the immediate postoperative period and slowly tapered over 6 months to 1 year.[11,32] Topical fluoroquinolone use until the removal of all sutures has also been shown to be effective for bacterial prophylaxis[20] given the high risk of infectious keratitis in the pediatric population coupled with difficulty examining and diagnosing an infectious keratitis in a pediatric patient. A study conducted by Wills Eye Hospital determined the administration of topical cyclosporine-A 2.0% drops 4 times a day for the first 3 months increases the likelihood of graft survival and may benefit higher risk patients and/or patients with repeat corneal transplant rejection episodes.[20,32] Cyclosporine 0.05% (Restasis) may also be used to prevent and treat rejection in high-risk patients, although may be less efficacious. Topical tacrolimus 0.1%, a more potent immunosuppressant, has also been proven to significantly reduce graft rejection with fewer adverse effects in comparison to cyclosporine.[42]

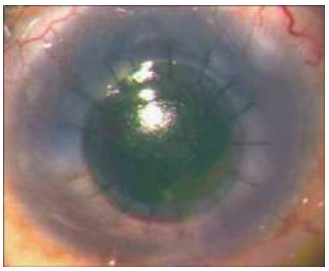
Suture Removal

Appropriate timing of suture removal is a complex and a crucial decision in pediatric patients after any type of keratoplasty. The healing process in pediatric penetrating keratoplasty is faster compared with adults, and safe and successful removal starting within 2 to 6 weeks during the postoperative period has been reported.[32] DiZazzo et al[11] suggest suture removal within 3 months of surgery in patients less than 8 years old and within 6 months for patients greater than 8 years old. A timeline outlined by O'Hara et al[1] involves removal at 4 to 6 weeks for patients less than 1 year old, 6 to 8 weeks for patients 1 to 2 years old, 8 to 12 weeks for patients 2 to 3 years old, and 12 to 16 weeks for patients 4 to 6 years old to compensate for the corneal healing which differs at different age ranges.

In children less than 6 months old, repeated examinations under anesthesia (EUA) are recommended in the early postoperative period until sutures are removed, followed by regular EUAs for 6 months before gradually reducing the frequency of examinations.[4] Although the timing of removal is not standardized, there is consensus in the immediate removal of loose or vascularized sutures to prevent rejection episodes or infectious keratitis.[11,14,32] In addition, the presence of suture microabscesses necessitates early suture removal as this reflects an inflammatory response, which may hasten graft rejection. Following suture removal, experts recommend an increased steroid and antibiotic therapy for a week after to decrease the increased risk of rapid rejection and infectious keratitis.[4,14,32]

Graft Rejection

Graft rejection occurs more rapidly and frequently following pediatric penetrating keratoplasty and is less responsive to treatment in comparison to adults.[11] Due to the robust immune response in pediatric patients, graft rejection is one of the major causes of graft failure in pediatric corneal transplants.[11,14] Long-term use of postoperative topical steroid therapy alone, or in combination with cyclosporine, can reduce this inflammatory response and potential for rejection.[11,43] Diagnosing graft rejection in pediatric patients is challenging as these patients are often unable to communicate concerns, pain, or visual changes, which contributes to a delay in diagnosis. Parents may present after noticing a decrease in visual acuity, hazy cornea, or redness in the postoperative eye. On routine examination, the physician may note signs of rejection which can include anterior segment inflammation with cell and flare, ciliary congestion, corneal edema, corneal vascularity, and/or opacity during a postoperative visit.[11,44]



The risk factors associated with transplant rejection in pediatric patients depend on the indication for surgery, presence of vascularization in the peripheral cornea, preoperative diagnosis of glaucoma, history of keratoplasty in the contralateral eye, and recipient age at surgery.[11] Patients less than 5 years of age at the time of surgery have a significantly higher rate (52.9%) of graft rejection–mediated graft failure compared with patients greater than 5 years old (22.2%).[9,14] The rate of graft rejection progressing to failure ranges from 11% to 50% but noted to be up to 63% of patients based on the risk factors as noted above.[11,45] Furthermore, posttransplant rejection reversal in pediatric patients is lower than adult patients, with only 28% of cases demonstrating resolution.[46] Although graft rejection can occur at any point, close monitoring of pediatric patients through EUAs in the following year after surgery is critical as rejection most commonly occurs within the first postoperative year.[29] Early detection and diagnosis of rejection through frequent postoperative examinations with or without anesthesia can improve chances of graft success.11 Chan et al[20] suggest weekly EUAs for the first months after surgery before shifting to monthly EUAs for the first year.

Graft Infection

Graft infection, also known as infectious keratitis, occurs in ~10% to 50% of pediatric postoperative cases.45 Streptococcus pneumoniae (39.7%) and Staphylococcus aureus (5.2%) are the 2 major causative organisms.[11,21] Pediatric patients have a greater risk of infection; consequently, close postoperative management is required. Early suture removal, particularly of loose or vascularized sutures, and prophylactic antibiotic therapy, including topical quinolones and polymyxin B-trimethoprim for the duration that the corneal sutures are in place, have been shown to minimize the risk of graft infection.[32] Xavier Dos Santos Araújo et al[45] proposed that 33% of infectious keratitis cases among pediatric postoperative patients were due to loose sutures. Graft infection can result in graft failure (9.1%); consequently, graft infection prophylaxis with topical antibiotics and early treatment can reduce this risk.

Glaucoma

Adequate control of IOP both preoperatively and postoperatively is vital for graft survival, preventing optic nerve damage, and optimizing visual acuity.45 Reported rates of glaucoma secondary to penetrating keratoplasty range from 5% to 25%, with a higher incidence in patients with Peters' anomaly.[11,35,47] Glaucoma has been found to be the only independent predictor of graft survival; thus, early detection via routine EUAs, IOP measurements, dilated optic nerve examinations, and axial length measurements is essential.[4,12,35] Treatment for glaucoma includes medical management, trabeculectomy with adjuvants, trabeculectomy. Glaucoma drainage implant procedures may also be effective in IOP control following pediatric keratoplasty but also can pose a risk to corneal integrity by contributing to endothelial cell loss.[48]

Amblyopia

Amblyopia detection, prevention, and treatment are important preoperative factors in determining surgical timing and a major postoperative concern following pediatric keratoplasty. The goal of effective amblyopia management is to obtain symmetric and ageappropriate visual acuity in both eyes to ensure the development of binocular fusion. Dana et al9 determined amblyopia to be the only independently significant prognostic factor for visual improvement after keratoplasty. Consequently, effective early detection and treatment of amblyopia is crucial to obtain favorable outcomes. For nonverbal children, recognizing abnormal eye movements, abnormal head posture, nystagmus can allow for the early detection of amblyopia.[11] Amblyopia therapy including patching, atropine drops, corrective glasses, or contact lens, should be initiated as soon as possible after appropriate healing of the corneal transplant is complete.[4,11,48]

Cataracts

Cataract formation following pediatric keratoplasty ranges from 2% to 7%; however, there is an increased incidence (18%) of cataract formation in patients who have undergone repeat surgical interventions.[4,12] Low et al[47] report a higher incidence of cataract following penetrating keratoplasty (20.5%) when compared with the rate of overall postoperative cataract formation (10.5%) in eyes that underwent penetrating keratoplasty, anterior lamellar keratoplasty, lamellar corneal patch graft and Descemet stripping automated endothelial keratoplasty. Similar to other postoperative complications, the robust inflammatory response in pediatric patients significantly increases the risk of cataract formation.[1] In addition, the increased likelihood of iatrogenic damage to the lens during surgery due to the shallow anterior chamber, in addition to the exposure of the lens to air tamponade, may contribute to cataract formation.[23] Finally, prolonged postoperative steroid use is also associated with posterior subcapsular cataract formation, however, the administration of topical cyclosporine has been reported to minimize this risk.[4]

Prognosis

Graft Survival Graft survival following pediatric keratoplasty is affected by several factors both preoperatively and postoperatively. The indication for transplantation, age at surgery, prior graft rejection episodes, glaucoma, and previous and concurrent operations impact graft survival. O'Hara et al[1] reports the indication for transplantation as one of the major key factors in graft outcome, which is supported by studies reporting

higher rates of graft survival among patients with acquired corneal opacities compared with patients with congenital corneal opacities.[32,43] However, this difference fails to reach statistical significance, which may be attributed to the varying study group sizes, heterogeneity of the groups, and variable followup periods.[4,13] The overall rate of graft failure in pediatric patients following penetrating keratoplasty is 33.8% with 50% of grafts failing within the first 26 weeks after surgery.[14] Graft rejection, particularly repeated rejection, is a major risk factor for graft failure and is associated with significantly worse survival rates.[10,32,45] Glaucoma, as discussed above, is associated with worse outcomes and is the only independent predictor of graft survival.[11,12,45] Consequently, patients without glaucoma, both preexisting and postoperative, demonstrated better 1-year survival as compared with patients with glaucoma.[10,12] Patients with previous and subsequent operations had no significant difference in graft survival.[12] However, in contrast, the combination of other procedures (ie, vitrectomy, lensectomy, glaucoma surgery) at the time of penetrating keratoplasty is associated with worse outcomes and a decreased rate of graft survival (38.5%) as compared with that of eyes without additional procedures (51.3%).[12,21,43]

Additional risk factors for poor graft survival include anterior segment dysgenesis, frequent graft failure requiring re-grafting of corneal tissue, corneal neovascularization, inflammation, aphakia or pseudophakia, and corneal ulceration.[1,9,32] Graft survival at 1 year is ~80% but has been reported to range from 35% to 82% and decreases slightly to 67% at 2 years.[9,20,32] Trief et al[32] determined the mean graft survival time in pediatric keratoplasty to be ~45.2 months.

Visual Outcome

Assessing visual outcomes following pediatric keratoplasty depends on a combination of graft clarity and amblyopia. Favorable visual outcomes are associated with acquired corneal opacities in older patients, as eyes with congenital opacities will be affected by preexisting deprivational amblyopia or other associated ocular anomalies.[32,45] Worse visual outcomes are associated with preoperative amblyopia, frequent graft failure, graft-related optical distortion, high postoperative astigmatism, and associated ocular pathology.[9] The role of surgical timing on visual outcomes is currently unknown, with studies showing better visual prognosis in younger patients and others citing no improvement of outcomes with earlier timing.[43,48] The rate of graft clarity has been found to be higher in patients with acquired nontraumatic opacities (70.6%), followed by congenital opacities (63.8%) and acquired traumatic opacities (54.5%).[14] In addition, eyes with acquired opacification have a greater probability (>70%) of remaining clear at 1 year following surgery compared with eyes with congenital opacification (60%).[8] The need for repeat corneal grafting results in a significantly decreased likelihood of graft clarity and earlier graft failure.[11] In general, visual acuity following pediatric keratoplasty improves significantly. In one study comparing congenital versus acquired opacities, there was a greater improvement in the acquired opacities group (P=0.0408). Eyes with acquired opacities, both nontraumatic and traumatic, have higher rates (58.3% and 66.7%, respectively) of achieving visual acuity of 20/400 or better after surgery compared with congenital opacities (33.3%).[14] This may be in part due to normal development of vision without any amblyogenic risk factors before corneal involvement.[45,48] There are less common outcomes where visual acuity may remain the same or worsen in some patients.[32,45] Anatomic success alone does not equate to good visual outcome in all patients following keratoplasty.[45] Poor visual acuity despite clear grafts is most often associated with irreversible amblyopia or postoperative irregular astigmatism.[14,45] In fact, amblyopia treatment is the only independently significant prognostic factor for visual improvement after surgery.[9] Consequently, amblyopia management, as outlined previously, is crucial to achieving favourable visual outcomes.

Conclusions

Pediatric corneal transplantation remains a challenging procedure with high risks and relatively poorer visual outcomes compared with adults. Several considerations must be made with respect to preoperative, intraoperative, and postoperative care in pediatric keratoplasty. Preoperative assessment includes appropriate patient selection, timing of surgery, and indications for the keratoplasty. Intraoperative considerations such as reduced scleral rigidity, smaller globe, and positive posterior pressure result in a more technically challenging procedure compared with adult keratoplasty. Postoperatively, there is a higher risk of graft rejection, glaucoma, and infection which can lead to worse visual outcomes. In addition, postoperative management of amblyopia is crucial for optimal visual rehabilitation after pediatric keratoplasty. Successful pediatric keratoplasty may be achieved with meticulous preoperative, intraoperative, and postoperative planning and care to optimize the visual development in patients with unilateral or bilateral corneal opacities.

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Corneal surgery in keratoconus: which type and which technique

- Dr. Varun Malhotra
Center for sight, Hyderabad.

Abstract:

Keratoconus is a disease characterized by progressive thinning, bulging, and distortion of the cornea. Advanced cases usually present with loss of vision due to high irregular astigmatism. A majority of these cases require surgical intervention. This review provides an update on the current treatment modalities of corneal surgery available for the management of advanced corneal ectasias.

Keywords: Keratoconus, Deep anterior lamellar keratoplasty, Penetrating keratoplasty, Corneal transplant, Rejection

Background Corneal graft is the traditional recourse for advanced keratoconus.[1] There are many different grading schemes for keratoconus from scales based on outdated indices such as the Amsler-Krumeich scale, to scales using a variety of detailed metrics of corneal structure provided by anterior segment optical coherence tomography and Pentacam imaging. All these different scales do not always correlate well with disease impact. While there are eyes with milder disease that may exhibit contact lens intolerances, there are other eyes with severe disease that obtain good functional vision with contact lenses. Therefore, although there is no precise definition for advanced disease, most specialists would agree that a keratoconus patient is eligible for corneal transplant when spectacle correction is insufficient, continued contact lens wear is intolerable, and visual acuity has fallen to unacceptable levels .[2] Nevertheless, there has been a strong push to extend other treatment modalities that were originally meant for mild to moderate disease such as ultraviolet crosslinking (UV-CXL) and intrastromal corneal ring segments (ICRS) to treat advanced disease. In 2014, Bowman Layer transplantation was also described for advanced keratoconus with extreme thinning/steepening.[3] These less troublesome therapeutic alternatives will seek to arrest disease progression, reenable comfortable contact lens, or improve visual acuity to some extent, although rarely do the visual gains exceed one or two lines in advanced disease. These techniques would permit penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) to be postponed or avoided entirely.[2] In general, despite the excellent outcomes of PK, DALK may be preferred in patients with keratoconus because of the absence of risk of endothelial rejection, earlier tapering of steroids, decreased risk of secondary glaucoma, and increased wound strength.[4] The advantage of DALK is even more evident in patients with mental retardation in which PK has a higher incidence of postoperative complications such as globe rupture, corneal ulceration and graft rejection, as well as in phakic patients, and corneas with significant peripheral thinning.[2] PK would be considered more suitable in cases where endothelial dysfunction is present or when deep corneal scarring severely affects the visual axis up to the Descemet membrane (DM) level. It is not unusual for keratoconus to coexist with endothelial dysfunction; it might be underestimated as stromal thinning of keratoconus may mask the corneal edema. Fuchs endothelial dystrophy is the most common of such disorders, but also include posterior polymorphous dystrophy, a peculiar condition of endothelial depletion and guttae excrescences that may be the product of the keratoconus itself rather than a distinct entity.[5] If central deep corneal scarring is present, PK will provide a better visual acuity than DALK, but with a higher risk. In some instances, safety of DALK can outbalance the better visual acuity of PK. In fact, when corneal scars arise from previous hydrops, PK outcomes tend to be worse as the risk of graft rejection is higher.[2] In these cases, manual lamellar dissection for DALK is a good choice as Anwar's big bubble technique is contraindicated owing to the high risk of perforation during surgery. While the scope of this article is mainly corneal grafting as treatment of keratoconus, it is important to point out that the main goal of treatment for keratoconus has changed over the last few years from that aiming to improve visual acuity with keratoplasty to a number of relatively new procedures

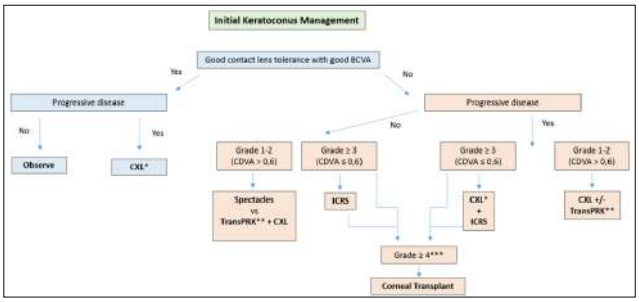


Figure. 1 Decision tree for intervention at presentation in keratoconus. Grading according to the RETICS classification.[1] (* if thinnest point > 370 µm; ** wavefront guided transPRK (limited treatment) to reduce coma-like aberrations and increase CDVA; *** if corneal scarring, insufficient corneal thickness for ICRS implantation or ICRS failure with persistent contact/scleral lenses intolerance and poor CDVA)

focused on the prevention of disease progression or to restore/support contact lens tolerance by making wearing more comfortable. These include UV-CXL, ICRS, and a newly proposed type of "corneal transplant" known as Bowman Layer transplantation described by Gerrit Melles.[3] In Fig. 1, we present our decision tree for intervention at presentation in keratoconus.

Review

A review of the literature on the topic of surgical treatment of keratoconus has received considerable attention and a formidable number and variety of surgical proce-dures even before keratoplasty was considered the most suitable procedure.[6] Surgical options that have been proposed include intraocular operations such as paracentesis of the anterior chamber, lens extraction or needling, or deviation of the pupil by incarcerating the iris in a corneal incision to achieve a stenopeic slit-like pupil; cone excision procedures; or flattening techniques by scar formation, brought by cauterization of the conus with chemicals, electrocautery, high frequency current or by splitting the DM.[6] Before keratoplasty became an option, Alfred Appelbaum in 1936.[7] stated concerning the surgical treatment of keratoconus, "Surgical intervention aims to produce flattening of the cornea in order to improve eyesight. When no degree of useful vision is obtained with the use of contact glasses, operative intervention may be considered – but no sooner. Only in cases of advanced or nearly hopeless conditions should the patient undergo operation. Most ophthalmologists agree with this. Too much cannot be expected of surgical treatment. At best, it gives a result far from ideal and none too lasting. The unsightliness which inevitably follows must be anticipated, and the appearance of the eye is always marred to some extent." Castroviejo, a Spanish ophthalmologist born in Logroño, Spain, performed the first PK for keratoconus in 1936.[6] in the Columbia Presbyterian Medical Center in New York. Several years later in an article about keratoplasty for the treatment of keratoconus, he concluded that keratoplasty was the only surgical procedure that fulfilled the two essential requirements for treating keratoconus: surgery had to be limited to the cornea, and the whole corneal protrusion had to be removed and replaced with normal tissue of normal curvature and thickness, leaving the pupillary area free of scarring.

Based on his experience, when a suitable technique was used, the percentage of permanently, greatly improved vision increased from 75 % to 90 %.[6] Lamellar keratoplasty (LK) was described earlier than PK. Although Arthur von Hippel performed the first successful LK in man in 1888.[8] decades earlier than the first successful human PK by Edward Zinn, Von Hippel's technique was abandoned in 1914 for PK and was not reintroduced until the 1940s.[9] However, the concept of deep LK extending down to DM is relatively new. Gasset reported a series of keratoconus patients in the late 1970s who received full-thickness grafts stripped of DM transplanted into relatively deep lamellar beds, and enjoyed good surgical results with 80 % of cases achieving 20/30 or better vision.[10] Dissection of host tissue 'close to' DM and the term 'deep lamellar keratoplasty' (DLK) in the conventional sense were first introduced by Archilla in 1984, who also showed the use of intrastromal air injection to opacify the cornea as a method to facilitate removal of host tissue.[11] Sugita and Kondo reported the first extensive study on the results of DLK compared with PK in 1997.[12] They showed that postoperative visual acuity was similar between DLK and PK with no episodes of immunological rejection in over 100 eyes. Despite the clear benefits of DLK, the classical technique of removing stroma layer by layer was at that stage time consuming and was greatly dependent on surgical experience. Only in the last two decades did DLK gain momentum thanks to improvement in surgical techniques and the availability of new surgical instruments and devices. The two most relevant papers on techniques were those from Melles and Anwar.In 1999, Melles described a technique to visualize corneal thickness and dissection depth during surgery,which created an optical interface at the posterior corneal surface by filling the anterior chamber with air completely.[13] In 2002, Anwar described his popular "big-bubble" technique in baring DM by injecting air into the deep stroma to create a large bubble between the stroma and DM.[14] Approximately about 12–20 % of the keratoconus patients may require a corneal transplantation.[15] The Australian Graft Report of 2012 shows that keratoconus,with almost 1/3 of the corneal grafts performed, was the first reason for keratoplasty, followed by bullous keratoplasty and failed previous grafts. The 2012 Eye Banking statistical Report published by the Eye Banking Associations of America found that keratoconus was the reason for PK in 18 % of the cases and in 40 % of the DALK cases. Surprisingly, PK represented almost 80 % of the total grafts while DALK only accounted for 3 % of the total keratoplasties done, meaning that time-consuming and surgical experience is still a factor reducing the popularity of DALK in the US. Increasingly, however, DALK is becoming the preferred surgical option, largely thanks to improvements in operative technique, and now representing 10–20 % of all transplants for keratoconus and 30 % when eyes with previous hydrops are excluded.[2] In the UK, the percentage of transplants for keratoconus in which DALK was used increased from 10 % in 1999–2000 to 35 % in 2007–2008.[16]

Penetrating keratoplasty in keratoconus

PK has traditionally been the surgery of choice for keratoconus, but nowadays lamellar techniques are the gold standard for patients with mild to moderate disease.

Currently, an elective PK is reserved for those advanced cases where the DM and endothelium appear splitted due to a previous corneal hydrops. Frequently, a previous hydrops is not clearly reported by the patient, but in absence of an obvious endothelial split, deep stromal scars involving the DM are observed. In such cases

a lamellar technique can still be attempted, mainly if these scars are not affecting the visual axis, but as the integrity of the DM is not intact any longer, this layer has a great tendency to rupture through the area of the scar (if and when a Big Bubble technique is used) and the surgery will need to be converted into a PK intraoperatively if a big tear is observed (longer than 2 to 3 clock hours). PK technique for keratoconus does not differ significantly from the technique used for other etiologies, but some considerations should be taken into account:

1. *Donor size*:

A 7.5–8.5 mm host trephine (in relation with the corneal horizontal diameter) is often used and centered with the optical axis. However, the cone in keratoconus is often inferiorly displaced and should be fully removed to avoid residual or recurrent disease.[17] Therefore, the extent of the cone should be well understood before surgery and thinning mapped out by slit lamp examination, as this will be difficult to discern with the operating microscope. Fleischer iron ring formation, which usually circumscribes the cone, may assist on its delineation. Corneal topography is not reliable in advanced scarred conus and should not be considered for surgical planning. Donor size will then be adjusted in relation with the host limbal white-to-white measurement and conus extension, so grafts larger than 8.5 mm may occasionally be needed in severe conus, as well as partial decentration respecting the optical axis in cases of very advanced conus with a severe thinning up to the perilimbal area. Yet, the risk of rejection increases with grafts larger than 8.5 mm in diameter and when the graft-host junction moves closer to the limbus, both of these which should be considered during post-operative treatment and management.[18,19] Decentered grafts can as well induce a significant irregular astigmatism into the visual axis that requires rigid lenses for visual rehabilitation of the patient and occasionally, a second centered graft for visual purposes.The donor tissue trephine is routinely sized at 0.25 mm larger than the host trephine because, using current techniques, donor corneal tissue cut with a trephine from the endothelial surface measures approximately 0.25 mm less in diameter than host corneal tissue cut with the same diameter trephine from the epithelial surface[20]. Keratoconus patients may benefit from using same-diameter trephines for both donor and host tissues, which undersize the donor button and helps to reduce postoperative myopia,[21,22] but the surgeon should be aware that obtaining watertight wound closure with an undersized donor tissue can be challenging and may require additional sutures. Moreover, a flattened corneal contour could complicate contact lens fitting in the anisometropic patient. Laser excimer ablation for correction of a significant residual hyperopia after PK may also not be possible as it is not as predictable and efficient as it is with residual myopia, which will require phakic or pseudophakic piggyback intraocular lenses for patients who are intolerant of spectacles and contact lenses.[23] Considering the above, although undersizing the donor cornea may provide better visual outcome in patients with keratoconus, it should be selected carefully in PK. Axial length can be an important factor in the refractive error outcome following PK.[24] Ultrasound axial length measured from the anterior lens capsule to retina reveals a broad range in length from 18.77 to 25.65 mm. Reducing donor size, in a relatively short eye, could result in significant postoperative hyperopia, so same-size donor and host corneal buttons should not be used when the anterior lens-to-retina length is less than 20.19 mm, the mean length for non-keratoconic individuals with emmetropia.

2. *Suturing technique*:

Once the four cardinal 10-0 nylon sutures have been placed, the surgeon can use any of these preferred suture techniques: interrupted sutures (IS), combined continuous and interrupted sutures (CCIS), single continuous suture (SCS) or double continuous suture (DCS). IS should always be the closure method of choice in cases where a partial or complete suture removal in one region of the graft is likely to be necessary at some point during the postoperative period, examples include: pediatric keratoplasty (sutures becoming loose too quickly), vascularization in the host cornea (occasionally seen after a hydrops episode or contact lens related keratitis), multiple previous rejections or other inflammatory concomitant conditions that may predispose to localized vascularization, rejection, or ulceration of the donor tissue. Furthermore, large and decentered grafts that are placed close to the limbal area present an increased risk of rejection, thus making the use of IS necessary for its closure.

However, most of the keratoconic eyes do not present any additional risk for graft rejection or infection, so a SCS or DCS is generally preferred by most surgeons. The advantages of a continuous suture are ease of placement,the ease with which the suture can be removed at a later date, and the potential for suture adjustment intrasurgically (with an intraoperative keratometer) and postoperatively to reduce astigmatism. With DCS, a 12-bite 10-0 nylon suture placed with bites at approximately 90 % depth and a second continuous suture (10-0 or 11-0 nylon) placed with bites alternating between each of the original suture's bites for 360° at approximately 50–60 % corneal depth are used. The second suture is tied only with enough tension to take up slack in the suture. The second suture permits early removal or adjustment of the first 10-0 nylon suture for astigmatism control in 2–3 months; the second suture acts as a safety net if the deep suture breaks during the adjustment, and is generally left in place for 12–18 months postoperatively (Fig. 2).

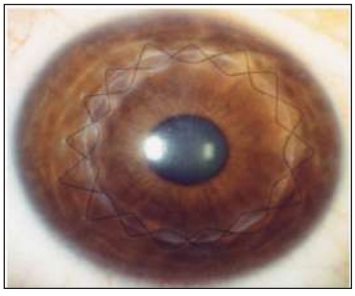


Figure. 2
Slit-lamp image of a keratoconic eye after penetrating keratoplasty with a double continuous suture

IS, CCIS, and SCS have shown comparable postoperative astigmatism [25]. In addition, a comparison of astigmatism in keratoconus patients utilizing a single continuous versus a DCS showed that after suture removal, astigmatism between the two groups was comparable (DCS − 4.6 D, SCS − 5.2 D).[26] Therefore, it is apparent that all methods of suture closure can work well. The ultimate choice rests with the surgeon.

Regardless of the preferred method, it is very important to have a clear concept of each suture technique. To give a basic idea for standard graft suturing, the needle is passed 90 % depth through the donor cornea and then through the host cornea. The ideal bite is as close to DM as possible, and there should be an equal amount of tissue purchased in the donor and host cornea in order to approximate Bowman's layer in both the donor and host. Discrepancies frequently exist in the thickness of the donor and host corneas either when donor corneas are thick due to the hyperosmolar glycosaminoglycans in the preservation medium or fresh donor tissue is used in patients with severe corneal edema. This scenario is frequent in keratoconic eyes where the graft is sutured to a relatively thin host cornea. Closing Bowman's layer to Bowman's layer should always be attempted to avoid steps in the graft-host junction and subsequent exposed sutures. Therefore, in areas where the recipient cornea presents thin (assessed preoperatively by slit lamp examination) partial thickness bites (50–70 % depth) in the donor tissue should be in relation with deep bites (95 % depth) in the host thin stroma (Fig. 3).

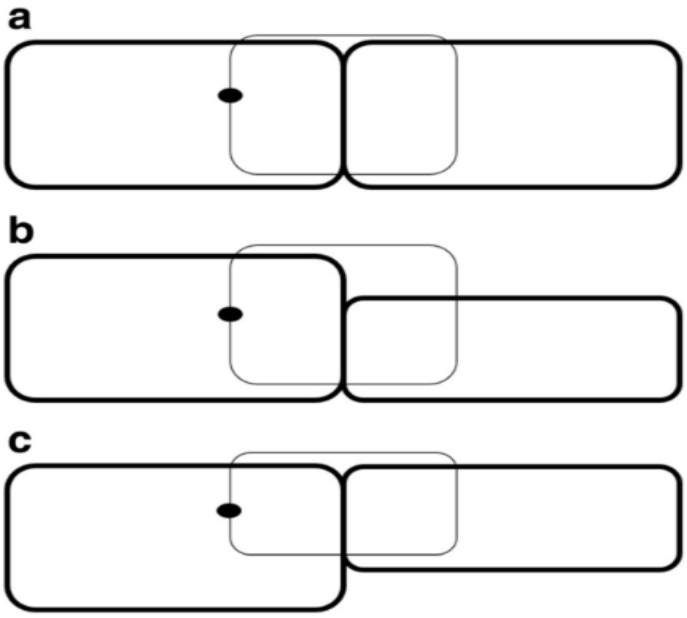


Figure. 3 Graft-host junction alignment after suturing. Normal appearance of the graft-host junction with correct aligning of Bowman's layer of the donor and host corneas, with needle passed at a 90 % depth on both sides (a). If care is not taken in cases of a thin recipient cornea, steps will remain at the graft-host junction, leaving an irregular astigmatism and exposed sutures that need to be replaced (b). To avoid this, a partial thickness bite (50–70 % depth) should be performed at the donor side (c)

The postoperative astigmatism management and elective suture adjustment/removal for PK in cases of previous keratoconus do not differ from other PK indications. A complete suture removal is generally recommended after 12–15 months.

3. *Outcomes*:

PK offers good long-term visual rehabilitation for keratoconus patients. Compared with other indications for PK, there is a relatively low rate of graft failure and long mean graft survival. Rejection rate has been reported to be 5.8–41 % with a long term follow-up with most rejections occurring in the first 2 years.[27-31] Larger host trephine size, male donor gender, and non-white donor race have been associated with increased rejection hazard.[27]. Despite this observed rejection rate, only a 4–6.3 % graft failure rate has been reported with a mean follow-up of 15 years, and with an estimated 20 year probability of 12 % .[27,28,32] Fukoka et al. reported a cumulative probability of graft survival at 10, 20, and 25 years after PK of 98.8, 97.0 and 93.2 %, respectively, while Pramanik et al. estimated a graft survival rate of 85.4 % at 25 years after initial transplantation.[28,32] Taken together, the existing evidence show that graft survival rate gradually decreases after 20 years post-PK.

An average best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (Log-MAR) at preoperation, 10, 20, and 25 years after surgery of 1.54 ± 0.68, 0.06 ± 0.22, 0.03 ± 0.17, and 0.14 ± 0.42, respectively, have been reported [28]. Best spectacle-corrected visual acuity (BSCVA) of 0.14 ± 0.11 LogMAR has been reported with a mean period of 33.5 months, while a BSCVA of 20/40 or better with a mean follow-up of 14 years was observed in 73.2 % of patient.[31,32] An open angle glaucoma rate of 5.4 % with a mean follow-up of 14 years has also been reported.[32] Claesson et al. reported a poorer survival and worse visual outcome of regrafts compared with first grafts in patients where the original indication was keratoconus:the failure rate was three times higher with regrafts and the observed visual acuity with preferred correction was ≥ 0.5 in 69 % of first grafts while only 55 % of regrafts achieved that level.[33]

Deep anterior lamellar keratoplasty(DALK) in keratoconus

The goal of deep lamellar anterior keratoplasty in keratoconus is to achieve a depth of dissection as close as possible to DM. There are various ways to create a plane of separation between DM and the deep stromal layers mainly through variations of the two basic strategies: the Anwar big bubble method and the Melles manual dissection.

Surgical techniques

1. The big bubble method-Anwar based the big bubble method on a discovery in 1998 that intrastromal injection of balanced salt solution (BSS) was often effective at establishing cleavage plane just above DM.[34] This takes advantage of the loose adhesion between DM and the posterior stroma. Anwar and Teichman later described the current big bubble procedure in 2002 using air instead of BSS.After a partial trephination of 70–80 % of the corneal stroma, pneumatic pressure is used to detach DM by injecting air into the deep stroma with a 30G needle.The air injected into the stroma produces a dome shaped detachment of DM that is seen under the surgical microscope as a ring, which signifies that the big bubble has been formed. The stromal tissue above the DM plane is removed with spatula and scissors, making sure to first exchange the air in the supradescemetic plane with viscoelastic to avoid inadvertently puncturing the DM. When all of the stromal tissue is successfully removed, the DM exposed should be characteristically smooth (Fig. 4).

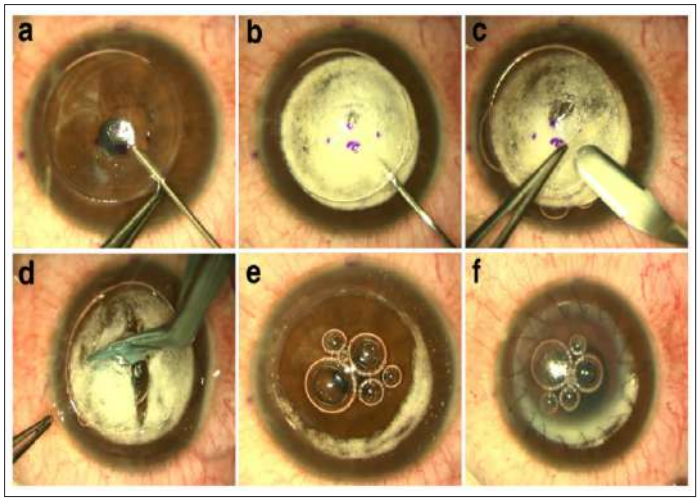
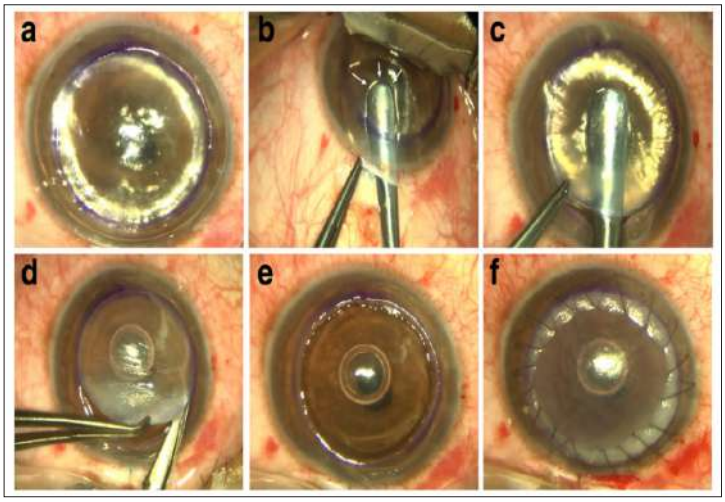


Figure. 4 DALK Big Bubble Technique. After a partial trephination of 70–80 % of the corneal stroma 30 G needle (a). Once the air is injected, it produces a dome-shaped detachment of the DM that is seen under the surgical microscope as a ring meaning that the big bubble has been formed (b). A lamellar dissection with a Crescent blade of the anterior stroma is then performed (c) followed by the removal of the stromal tissue above the DM plane with spatula and scissors (d), making sure to first exchange the air in the supradescemetic plane with viscoelastic to avoid puncturing DM inadvertently. When all of the stromal tissue is successfully removed, the DM exposed is characteristically smooth (e), and the donor cornea without its DM and endothelium is then sutured with the preferred suture technique (f)

2. Melles manual method-This technique is based on the air-endothelium interface [13]. First, the anterior chamber is filled with air.Then, using a series of curved spatulas through a scleral pocket, the stroma is carefully dissected away from the underlying DM. The difference in refractive index between air and corneal tissue creates a reflex of the surgical spatulas, and the distance between the instrument and reflex is used to judge the amount of remaining cornea. Viscoelastic is injected through the scleral incision into the stromal pocket. Once the desired plane is reached, the superficial stroma is removed using trephine and lamellar dissection (Fig. 5).

Figure. 5 DALK Melles Technique. First, the anterior chamber is filled with air and a partial trephination of 70 % of the corneal stroma is performed (a).Then, using a series of curved spatulas through a scleral pocket, the stroma is carefully dissected away from the underlying DM (b). The difference in refractive index between air and corneal tissue creates a reflex of the surgical spatulas, and the distance between the instrument and reflex is used to judge the amount of remaining underlying tissue (B, arrows). Viscoelastic is injected through the scleral incision into the stromal pocket and the dissection can be completed through the trephination edge (c). Once completed, the superficial stroma is removed (d), the DM exposed e, and the donor cornea sutured (f)



Over the years, there have been many variations to the standard technique. Lamellar dissection can be made with a diamond knife, nylon wire, microkeratome.[35] or femtosecond laser. To help in guiding the dissection plane, trypan blue, ultrasound pachymetry[36] or real time optical coherence tomography[37] (OCT) has been used. Partharsathy et al. describe a “small bubble” technique for confirming the presence of the big bubble.[38] For corneas with extreme peripheral thinning, a modified procedure has been proposed dubbed “tuck-in lamellar keratoplasty”[39,40] In this technique, the central anterior stromal disc is removed and a centrifugal lamellar dissection is performed using a knife to create a peripheral intrastromal pocket extending 0.5 mm beyond the limbus. The donor cornea is prepared in such a way that it has a central full thickness graft with a peripheral partial thickness flange. The edges of a large anterior lamellar graft are tucked in below to add extra thickness.

Outcomes

Most studies have found equivalent visual and refractive results between PK and DALK, although 20/20 vision seems more likely after PK [16, 41], provided that stromal dissection reaches the level or close to the DM.[16,41-46] For instance, in a recent study consisting Australian patients, which included 73 consecutive patients with keratoconus, the mean BCVA was not significantly different for DALK (0.14 logMAR, SD 0.2) versus PK (0.05 logMAR, SD 0.11).[16,41] A review of published literature that included 11 comparative studies on DALK and PK found that visual and refractive outcomes were comparable if the residual bed thickness in DALK cases were between 25 and 65 µm.[4]

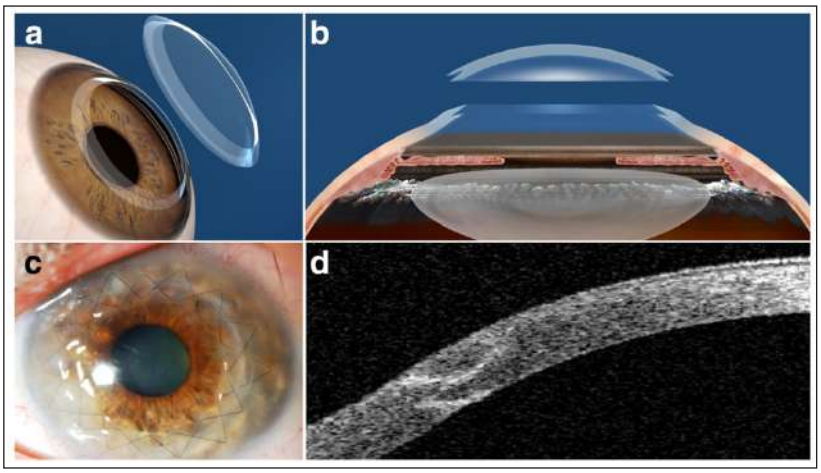


Figure. 6 Femtosecond laser assisted penetrating keratoplasty with a "Zig-Zag" edge profile (a, b: courtesy of Abbott Medical Optics, USA). Postoperative clinical picture (c) and an anterior segment OCT capture (d) where it is possible to appreciate the zig-zag edge profile at the host-donor interface with a perfect coalescence of the edges

In studies where the visual outcomes of DALK where inferior to PK,[47] the dissection plane was "pre-escemetic" and the incomplete stromal dissection and the not fully baring of the DM had a negative impact on the results.[47] The problem seems to be related to the depth of the undissected stromal bed rather than to its smoothness as pre-descemetic DALKs performed by laser ablation did not outperform those dissected manually. The recently published Australian graft registry data compared the outcomes of PKs and DALKs performed for keratoconus over the same period of time and found that overall, both graft survival and visual outcomes were superior for PK. In a recent study from the UK,

Jones et al. compared the outcomes after PK and DALK for keratoconus.[16] The risk of graft failure for DALK was almost twice that for PK. In day-to-day clinical practice, visual outcomes with DALK although comparable with PK, may be slightly inferior or less predictable compared with PK, given surgical inexperience, and unpredictable issues with respect to residual stromal thickness and DM folds. Nonetheless, elimination of risk of endothelial rejection compensates for this difference.Lastly, one of the important advantages of DALK is a lower rate of endothelial loss compared with PK. The reported endothelial cell loss is as high as 34.6 % after PK, whereas for after DALK, cell loss was only 13.9 %.[48]

Use of femtosecond laser in corneal graft for keratoconus

In the last decade, the femtosecond laser is one of the most important innovations in corneal transplant surgery for keratoconus. The laser allows the surgeon to focus the laser energy at a particular depth and then rapidly cut the tissue at that depth without causing any additional injury to the surrounding tissue. This permits doing lamellar dissection with high precision and also allows the surgeon to pattern these cuts into shapes (often referred to as mushroom or zig zag) creating a highly precise incision resulting in a perfect match of the donor tissue and the host tissue and a stronger junction and quicker visual recovery.[49] (Fig. 6).

Complications -

Allograft reactions are less frequent in DALK than in PK and less likely to result in graft failure if correct treatment is administered. Subepithelial and stromal rejection after DALK has been reported to be in the range of 3–14.3 % whereas in PK, it ranges from 13 to 31 % in the first 3 years after surgery.[2] Endothelial rejection is not an issue in DALK.

Increases in intraocular pressure (IOP) following DALK has been reported in 1.3 % of operated eyes,compared with 42 % of eyes after PK.[48] Development of glaucoma may also be up to 40 % less than PK.[50]; it is attributed to the lower steroid requirement of DALK.[51]

Urretz-Zavalia Syndrome was first reported following PK in keratoconus. It causes fixed, dilated pupil with iris atrophy that is a rare entity following DALK.[52] There are also a few complications that are unique to DALK and the presence of a donor-host interface. One of the major problems with DALKs is intraoperative DM perforation, which may occur in 0–50 % of the eyes,[2] which has also been described to occur weeks after an uneventful surgery.[53] Surgeon's inexperience, corneal scarring near the DM, and advanced ecta-sias with corneal thickness less than 250 µm increase this risk.[54,55] Depending on the size of the perforation, conversion to PK may be required to avoid double anterior chamber and persistent corneal edema,especially when the rupture leads to the collapse of the anterior chamber (macroperforation). Incidence of pseudo anterior chamber or double anterior chamber is in the range of 1 %.[56] It can occur because of retention of fluid secondary to breaks in the DM or because of incomplete removal of viscoelastic in the interface.[57] Large

pseudo chambers must be managed surgically by drainage of the fluid and anterior chamber injection of air or gas,[58] while small pseudo chambers normally end up resolving spontaneously.[59] The presence of DM folds caused by a mismatch between donor button and the recipient bed is usually transient and would disappear over time, but interface wrinkling when central and persistent may affect quality of vision.[60] Occasionally, an eye with an anatomically correct DALK may require a secondary reoperation to interface haze and poor visual acuity, usually stemming from incomplete or pre-descemetic stromal dissection.[2] Interface keratitis is a serious complication of DALK and its caused mainly by Candida,[61] but Klebsiella pneumonia[62] and nontuberculous mycobacteria[63] have also been isolated in several cases.Conservative treatment is usually unsuccessful and most cases need a therapeutic PK.[61] Interface vascularization can occur because of inflammatory,infective, and traumatic episodes which can be treated with bevacizumab injection.[64]

Keratoconus recurrence after corneal transplantation

We have already discussed the beneficial long-term results of the different options of corneal grafting for keratoconus. de Toledo et al. observed a progressive increase of keratometric astigmatism in 70 % of their cases from 10 years after suture removal, following an initial phase of refractive stability during the first 7 years after PK for keratoconus (4.05 ± 2.29 D 1 year after suture removal, 3.90 ± 2.28 D at year 3, 4.03 ± 2.49 D at year 5, 4.39 ± 2.48 D at year 7, 5.48 ± 3.11 D at year 10, 6.43 ± 4.11 D at year 15, 7.28 ± 4.21 D at year 20, and 7.25 ± 4.27 D at year 25), suggesting that a late recurrence of the disease may occur with an increasing risk over time.[17] Actually, a 20 year post-PK probability of 10 % have been reported previously, with a mean time to recurrence of 17.9–21.9 years. Given the younger age at which keratoconus patients undergo corneal transplantation, these long-term findings should be explained to patients and incorporated into preoperative counselling.[27,32,65] (Figure. 7).

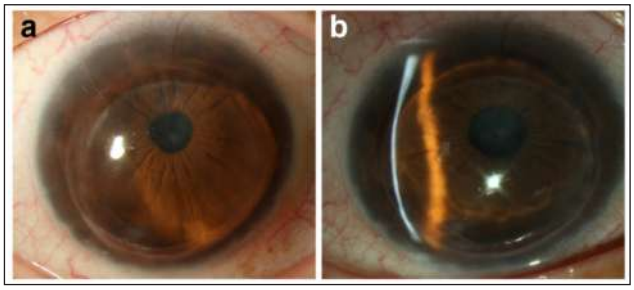


Figure. 7 Keratoconus recurrence. Slit lamp image of the recurrence 17 years after a penetrating keratoplasty (a). Observe the severe thinning of the recipient stroma at the graft-host junction (b) It is well known how other corneal stromal dystrophies such as granular or lattice dystrophy tend to recur into the donor cornea due to either colonization of the new stroma by the abnormal host keratocytes or epithelial secretion in the early stages.

In keratoconus, this host keratocyte invasion has not been well proven to be the main etiology for the post graft recurrent ectasia,but is likely to be related to the early keratoconic changes observed in the histology of explanted donor buttons after regrafting.[65-67] Post-graft ectasia is often preceded by thinning of the recipient stroma at the graft-host junction, so disease progression at the host stroma is likely to be the underlying reason for these cases of recurrent ectasia and progressive astigmatism.[17,65] In such cases, a mean keratometric sphere and cylinder increase of 4D and 3D, respectively, between final suture removal and diagnosis can be observed.[65]

The management of recurrent ectasia after corneal grafting should be spectacle adjustment if low stigmatism levels are induced, and rigid/hybrid gas permeable contact lenses with higher levels of astigmatism or significant anisometropia. For more advanced cases, scleral lenses may be considered before a surgical approach. If a second corneal transplant is required, either a new full thickness PK versus LK can be considered. Large grafts are usually necessary as the whole area of thinning should be included within the graft limits in order to excise the whole cone to avoid a new recurrence and also to avoid suturing through a thin recipient cornea. As large grafts are associated with increased risk of rejection and glaucoma, lamellar techniques by manual dissection of the host and donor corneal stroma are always preferable as far as the donor endothelium presents healthy without signs of failure. If femtosecond dissection of the lamellar bed is chosen, gentian violet and cyanoacrylate glue can be used in the area of thinning as masking agents to minimize the risk of perforation.[68] Limbus may have to be recessed while suturing very large grafts that sit close to the limbus in order to avoid passing the suture through the host's conjunctiva. Recurrence after regrafting has also been reported, so much so that it may require a third graft for visual rehabilitation.[65] Keratoconus recurrence after DALK has not been described. Very little evidence about its real incidence and impact is currently available. Feizi et al. reported a case where keratoconus recurred only 49 months after DALK.[69] They suggested that the time interval from transplantation to recurrence may be shorter after DALK than after PK, but this has not been supported or confirmed by other authors.[70] Further studies analysing the long term outcomes after DALK for keratoconus is required in order to assess its impact.[68]

A glance into the future

Keratoconus is a corneal disease that primarily affects the corneal stroma and Bowman's layer. Current research and future therapeutic directions are focusing on the regeneration of corneal stroma by little to no invasive procedures to avoid the common complications that we still see even with LK techniques. In the last few years, various studies have shown that CXL may offer some promise in slowing the progression of the disease.[71,72] New modalities of CXL are being explored to improve

the outcomes. CXL along with topography-guided photorefractive keratectomy (PRK) in order to provide better visual rehabilitation in patients with keratoconus is already being used.[73] A novel approach to enhance riboflavin penetration is based on iontophoresis, a non-invasive system aimed to enhance the delivery of charged molecules into tissues using a small electric current. It has been shown that an iontophoresis imbibition lasting 5 min achieves a sufficient riboflavin concentration in the corneal stroma for CXL treatment, with the advantage of shortening the imbibition time while pre-serving epithelial integrity.[74] Accelerated CXL was introduced in clinical practice in order to shorten the time required for a CXL procedure.[75] This technique is based on the Bunsen-Roscoe law of photochemical reciprocity. That is, the same photochemical effect can be achieved with reducing the irradiation interval provided that the total energy level is kept constant by a corresponding increase in irradiation intensity. In this modality, pulsed accelerated corneal collagen crosslinking seems to be more effective than continuous light accelerated corneal collagen cross-linking.[76] Melles at al. recently described a new technique where an isolated Bowman's layer is transplanted into a mid-stromal manually dissected corneal pocket in patients with an advanced (Stage III-IV) keratoconus.[77] They observed a modest improvement in the maximum keratometry and BSCVA, but an unchanged best contact lens corrected visual acuity (BCLVA). This is a new and interesting approach that could have its indication for those advanced keratoconus unsuitable for corneal collagen crosslinking or intracorneal ring segments and intolerant to contact lenses, but without visually significant corneal scars and therefore good BCLVA. In such cases, Bowman's transplant could avoid or postpone the necessity of keratoplasty if the mild observed corneal flattening enables continued contact lens wear and the cone is stabilized (as it has been reported to happen,but only with a sample of 20 eyes and a short mean follow-up of 21 months). Further research by alternative authors with a larger sample and longer follow up is needed before introducing this technique into routine clinical practice.As discussed, Bowman's transplantation could have some benefits in cases of advanced keratoconus, but even if these results are finally confirmed by other authors, they offer a mild improvement to these patients without a significant functional/anatomical rehabilitation. Thus, further techniques may focus on attempting the subtotal regeneration or substitution of the corneal stroma in order to achieve better results. Different types of stem cells have been used in various ways by several research groups in order to find the optimal procedure to regenerate the human corneal stroma: Corneal Stromal Stem Cells (CSSC), Bone Marrow Mesenchymal Stem Cells (BM-MSCs), Adipose Derived Adult Mesenchymal Stem Cells (ADASCs), Umbilical Cord Mesenchymal Stem Cells (UCMSCs), and Embryonic Stem Cells (ESCs).[78] These approaches can be classified into four techniques:

A. Intrastromal injection of stem cells alone:

Direct injection of stem cells inside the corneal stroma has been assayed in vivo in some studies, emonstrating the differentiation of the stem cells into adult keratocytes without signs of immune rejection. Our group showed the production of human extracellular matrix (ECM) when human ADASCs (h-ADASC) were transplanted inside the rabbit cornea.[79] Du et al. reported a restoration of the corneal transparency and thickness in lumican null mice (thin corneas, haze and disruption of normal stromal organization) 3 months after the intrastromal transplant of human CSSCs. They also confirmed that human keratan sulphate was deposited in the mouse stroma and the host collagen lamellae were reorganized, which led to the conclusion that delivery of h-CSSCs to scarred human stroma may alleviate corneal scars without requiring surgery. [80] Very similar findings were reported by Liu et al. using human umbilical mesenchymal stem cells (UMSCs) in the same animal model.[81] Recently, Thomas et al. found that in a mice model for mucopolysaccharidosis, transplanted human UMSC participate both in extracellular glycosaminoglycans (GAG) turnover and enable host keratocytes to catabolize accumulated GAG products.[82] In our experience, the production of human ECM by implanted mesenchymal stem cells occurs, but not quantitatively enough to be able to restore the thickness of a diseased human cornea. However, the direct injection of stem cells may provide a promising treatment for corneal dystrophies including keratoconus, via the regulation of abnormal host keratocyte collagen production to enable collagen microstructure reorganization and corneal scarring modulation.

B) Intrastromal implantation of stem cells together with a biodegradable scaffold:

In order to enhance the growth and development of the stem cells injected into the corneal stroma, transplantation with biodegradable synthetic extracellular matrixes (ECMs) has been performed. Espandar et al. injected h-ADASCs with a semisolid hyaluronic acid hydrogel into the rabbit corneal stroma. They report better survival and keratocyte differentiation of the h-ADASCs when compared with injection alone.[83] Maet al. used rabbit adipose-derived stem cells (ADSCs) with a polylactic-coglycolic (PLGA) biodegradable scaffold in a rabbit model of stromal injury and observed newly formed tissue with successful collagen remodelling and less stromal scarring.[84] Initial data show that these scaffolds could enhance stem cell effects over corneal stroma, although more research is required.

C) Intrastromal implantation of stem cells with a non-biodegradable scaffold:

At the present moment, no clinically viable human corneal equivalents have been produced by tissue engineering methods. The major obstacle to the production of a successfully engineered cornea is the difficulty with reproducing (or at least simulating) the stromal

architecture. The majority of stromal analogs for tissue engineered corneas have been created by seeding human corneal stromal cells into collagen-based scaffoldings, which are apparently designed to be remodeled (see Ruberti et al. 2008 for a general review of corneal tissue engineering).[85] The major drawback of these analogs is their lack of strength, thus unable to restore the normal mechanical properties of the cornea. New and improved biomaterials compatible with human corneas and with enhanced structural support have been developed leading to advanced scaffolds that can be used to engineer an artificial cornea (keratoprosthesis).[78] The combination of these scaffolds with cells can generate promising corneal stroma equivalents, and some studies have already been published that use mainly corneal cell lines providing positive results regarding adhesion and cellular survival in vitro.[86]. Our opinion is that stem cells do not differentiate properly into keratocytes in the presence of these synthetic biomaterials. Doing so makes them lose their potential benefits and not resolve the major drawbacks with such substitutes: their relatively high extrusion rate and lack of complete transparency.[87]

D) Intrastromal implantation of stem cells with a decellularized corneal stromal scaffold:

The complex structure of the corneal stroma has not yet been replicated, and there are well-known rawbacks to the use of synthetic scaffold-based designs. Recently,several corneal decellularization techniques have been described, which provide an acellular corneal ECM.[88]

These scaffolds have gained attention in the last few years as they provide a more natural environment for the growth and differentiation of cells when compared with synthetic scaffolds. In addition, components of the ECM are generally conserved among species and are tolerated well even by xenogeneic recipients. Keratocytes are essential for remodeling the corneal stroma and for normal epithelial physiology.[89] This highlights the importance of transplanting a cellular substitute together with the structural support (acellular ECM) to undertake these critical functions in corneal homeostasis. To the best of our knowledge, all attempts to repopulate decellularized corneal scaffolds have used corneal cells,[90-92] but these cells have major drawbacks that preclude their autologous use in clinical practice (damage of the donor tissue, lack of cells and inefficient cell subcultures), thus the efforts to find an extraocular source of autologous cells. In a recent study by our group, we showed the perfect biointegration of human decellularized corneal stromal sheets (100 µm thickness) with and without h-ADASC colonization inside the rabbit cornea in vivo (Fig. 8a and b), without observing any rejection response despite the graft being xenogeneic.[93] We also demonstrated the differentiation of h-ADASCs into functional keratocytes inside these implants in vivo, which then achieved their proper bio-functionalization (Fig. 8c). In our opinion, the transplant of stem cells together with decellularized corneal ECM would be the best technique to effectively restore the thickness of a diseased human cornea such as that in keratoconus. Through this technique and using extraocular mesenchymal stem cells from patients, it is possible to transform allergenic grafts into functional autologous grafts, theoretically avoiding the risk of rejection.

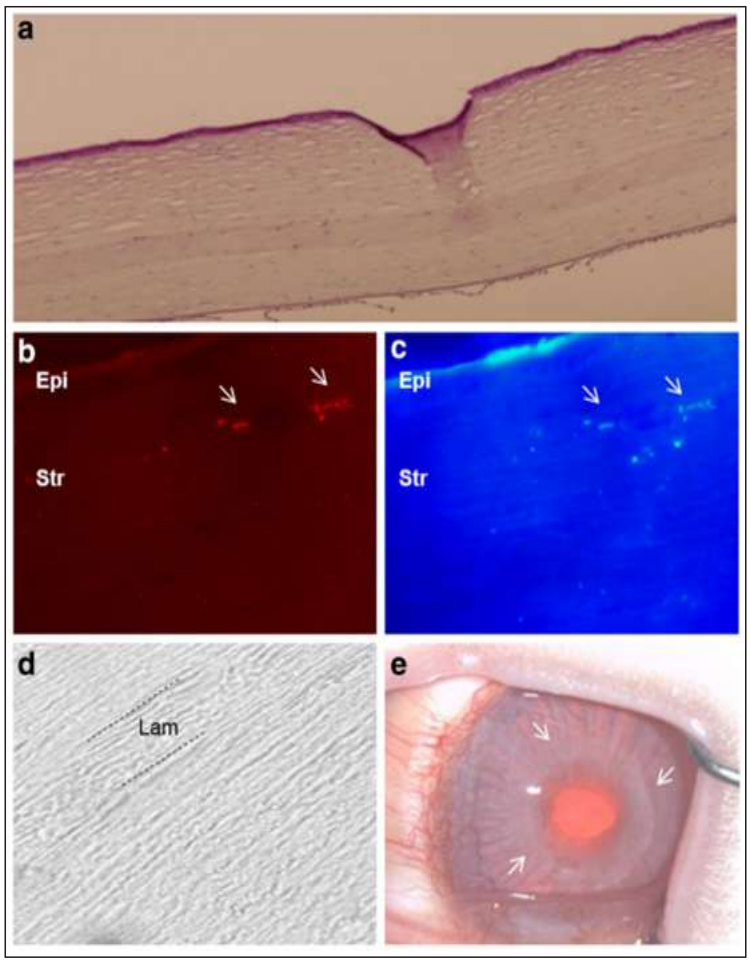


Figure. 8 Reconstruction of corneal stroma. a: Hematoxylin-eosin staining of a rabbit cornea with an implanted graft of decellularized human corneal stroma with h-ADASC colonization: hypocellular band of ECM without vessels or any inflammatory sign (magnification 200X); b: Human cells labeled with CM-DiI around and inside the implant that express (c) human keratocan (human adult keratocyte specific marker; magnification 400X), confirming the presence of living human cells inside the corneal stroma and their differentiation into human keratocytes (arrows); d: Phase-contrast photomicrographs showing a morphologically unaltered corneal stroma (magnification 400X); e: The graft remains totally transparent after 12 weeks of follow-up (magnification 2X) (arrows point to the slightly visible edge of the graft). Abbreviations: Epi: epithelium; Str: stroma; Lam: Lamina

Conclusion

Treatment of keratoconus has experienced great advances in the last two decades. From being limited only to rigid gas permeable contact lens wear and PK for the most advanced cases, to having different therapeutic alternatives currently to treat not only the cone and postpone/avoid the necessity of a corneal transplant, but also being able to halt the progression of the disease with a very high rate of efficacy and safety. Also, the advances in refractive surgery including surface corneal ablation treatments and phakic intraocular lenses have allowed a better management and visual rehabilitation of these patients after a corneal transplant is required, being able to achieve, in many cases, a 20/20 unaided vision. The future expected advances in transepithelial crosslinking, nanotechnology, and regenerative medicine predicts an exciting future in this field and we will be looking forward to updating these guidelines.

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Intra-operative Microscope integrated OCT based corneal lamellar surgeries

- Prof. Dr. Rohit Shetty[1], Dr. Yathish Shivanna[1], Dr. Harsha Nagaraj[1], Dr. Himanshu Matalia[2], Dr Nandini C[2].

[1]Department of Cornea and Refractive surgery, Narayana Nethralaya, 121/c, West of Chord Road, Rajajinagar, Bengaluru-560010, Karnataka, India.

[2]Department of Cornea and Refractive surgery, Narayana Nethralaya, #258/A, Narayana Health City, Bommasandra, Hosur Road, Bangalore - 560 099, Karnataka, India.

Introduction

Surgeries of cornea are complex and skill based and has long learning curve, especially for a beginner. Baffling corneal surgeries, especially lamellar, have often demanded a fair bit of intellect to comprehend the surgical skills, more so to the nascent surgeons. The latest in the armamentarium of corneal surgery involves corneal profile viewing intraoperatively, thereby enhancing the comprehension of complex corneal lamellar surgeries. Cutting edge technology like Microscope integrated intraoperative optical coherence tomography (MiOCT) would be a third eye for the young cornea surgeons as it acts as a guiding tool particularly in lamellar surgeries which makes surgery uneventful.

Microscope integrated optical coherence tomography (MiOCT) captures the real-time OCT images of the ocular tissue there by gives the ultrastructural view intraoperatively which aids in diagnosis and decision-making during surgery without the need to discontinue surgical maneuver. Ehler and his colleagues were the first to successfully use the MiOCT in ophthalmic surgery[1].

To our knowledge, three systems are currently commercially available in worldwide: Rescan 700 (Carl Zeiss Meditec, Germany), OPMedT (OPMedT, Germany), and Bioptigen/Leica EnFocus (Leica, Germany)[2,3].

We had experience with Rescan MiOCT (OPMI LUMERA 700 and RESCAN 700, Carl Zeiss, Meditec, Germany) in performing corneal surgeries.

Intraoperative OCT device is a commercially available platform, where OCT is fully integrated in the ophthalmic surgical microscope (Rescan 700, Carl Zeiss AG, Oberkochen, Germany). The platform is based on the Lumera 700 microscope, and the live OCT images can be projected in a heads-up fashion in one of the oculars. The OCT engine used is a Spectral Domain-OCT producing 27.000 A-scans per second. The light source used is a super-luminescent diode (SLD) with a central wavelength of 840 nm (bandwidth = 90 nm). The scan depth is 2.0 mm in tissue with an axial resolution of 5.5 lm and transversal resolution of 15 lm[4].

An extensive search on PubMed site was done using the following words: “Intraoperative OCT and corneal lamellar surgeries”. Twenty-four studies were identified. Out of 24, seven studies were excluded because they were not relevant to our paper. A total of Seventeen studies were included as they were significant. In the seventeen studies, three major review articles on MiOCT were found, out of which two articles were freely available. Indications of MiOCT were detailed in three articles. DALK procedure was assisted by MiOCT in four articles and complications related to DALK were managed using MiOCT in three articles. Photo image of big bubble in DALK surgery was documented in one article. Two articles published the use of MiOCT in endothelial keratoplasty. One publication also evidenced the use of MiOCT in intrastromal tattooing procedure.

The feasibility of MiOCT in ocular surgeries was assessed in the DISCOVER study. Almost in all the cases, the MiOCT device could successfully capture the necessary image. The use of MiOCT guided the operating surgeon in decision making and changed the surgical approach in 44% of anterior segment surgeries and 36% of posterior segment surgeries[5].

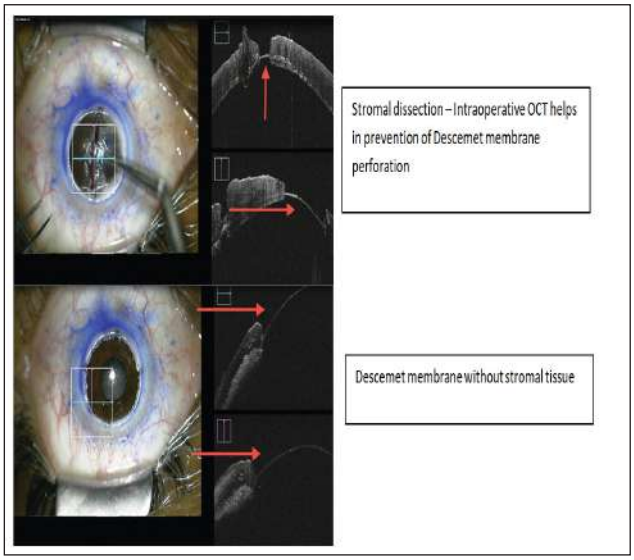
Deep anterior lamellar keratoplasty (DALK)

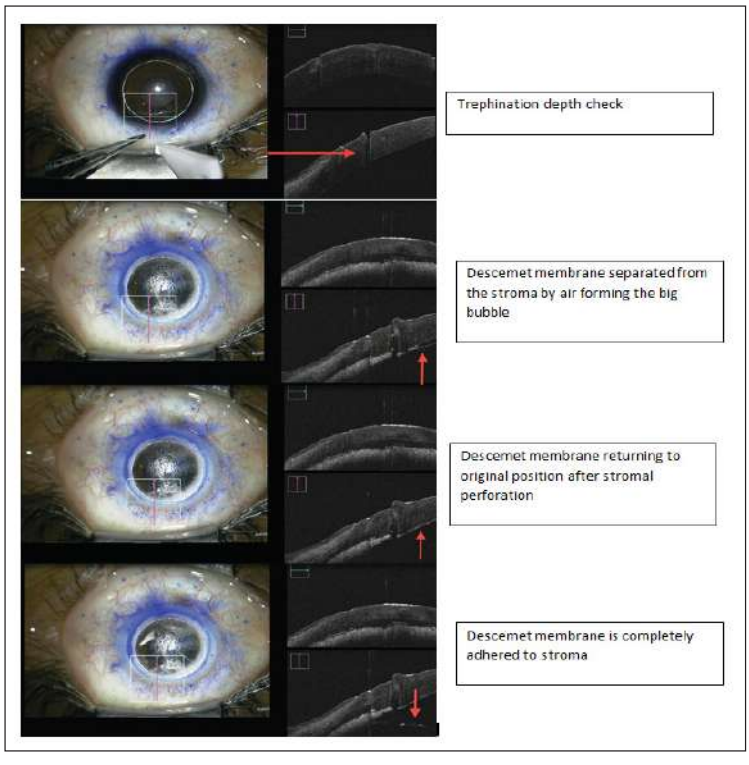
MiOCT is a useful tool both during intraoperatively and to monitor any post operative complications of DALK. MiOCT identifies the depth of stromal lamellar dissection, quantifies the depth at which air cannula reaches to achieve big bubble and guides in repositioning of cannula if required[6,7], determines the trephination depth in scarred irregular thinned corneas to achieve a big bubble and

thus helpful in avoiding corneal perforation. In addition, also useful for assessing the location of the DM and assessing bare DMs thus influencing the success of DALK. MiOCT also influences the parameters for the laser cuts at desired depth for the successful big bubble formation using femtosecond laser assisted Study by Scorcia et al showed that MiOCT was helpful in quantifying the depth (100microns from internal surface of cornea) at which cannula can be reached to achieve a successful big bubble and in almost 70% eyes, big bubble formation was seen[6]. MiOCT is also useful in guiding manual dissection in cases of failed big bubble, ensuring a thin and even residual stromal bed to achieve an optimal visual outcome[8].In Corneas with irregular scarring and thinning, the MiOCT helps to determine the initial trephination depth so as to avoid a perforation and to reach an adequate depth to achieve a big bubble which is well documented in the case series published by De Benito-Llopis et al[8].Singh and Liu et al revealed that realtime OCT helps in the visualization of creating the stromal tunnel of the desired length, width, and depth for pneumatic dissection thus making the femtosecond laser assisted DALK more safe, precise, controlled and thus makes the big bubble step more reproducible.[9,10]

Complications of DALK- Sharma et al have published a case report in which the continuous use of MiOCT in determining the location of the needle (to lie beneath the DM) helped in managing a case of DMD following DALK. In this case the MiOCT determined the height and position of DMD, position of needle thus helping in descemetopexy, noting the successful resolution of DMD after gas injection, also noted the presence of fluid between the posterior stroma and DM thus helpful in making the surgical decision of stab incision for removal of interface fluid[11].Another case report by Selvan et all have shown the successful use of MiOCT for guiding the management of triple chamber after DALK by fluid drainage with intracameral air tamponade with demonstration of Dua's layer.[12]

One more case by Chaniyara et al have well documented the successful management of a traumatic wound dehiscence in post DALK patient with descemetopexy with air along with wound dehiscence repair under the guidance of MiOCT. They also showed that the real-time images of was greatly helpful for intraoperative assessment of graft–host interface, graft host junction and the status of Descemet's membrane during the surgery.[13]



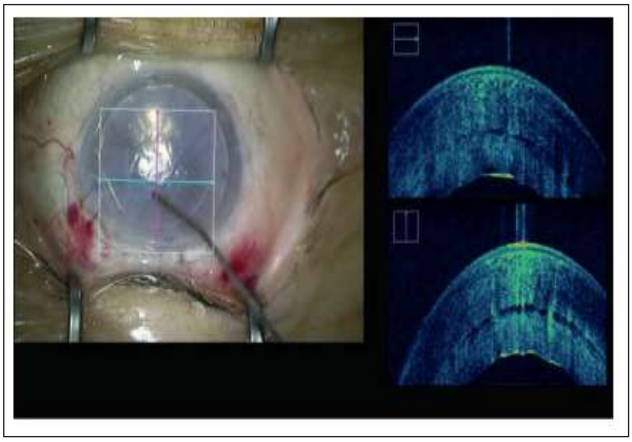


DSAEK

During DSAEK MiOCT helps in direct viewing of relationship between the graft and the host cornea, in assessing graft host interface width, any fluid in interface and graft thickness at various time points during and after the surgery and finally the graft adherence to stroma[14,15].

Steverink et al have evidenced that, the use of MiOCT led to the improvement in surgical decision making in assessing graft–host interface in DSAEK and identification of persisting interfaces which was undetectable by the surgical microscope and these persisting interfaces could have led to a higher rate of detachment and dislocation if left untreated. Thus,MiOCT is valuable in making DSAEK surgery anatomically successful by documenting the graft attachment to host[15].

Publications by Shazly et al and Pasricha et al proved that MiOCT is an invaluable tool in performing DSAEK for severe opaque cornea cases.[16,17]



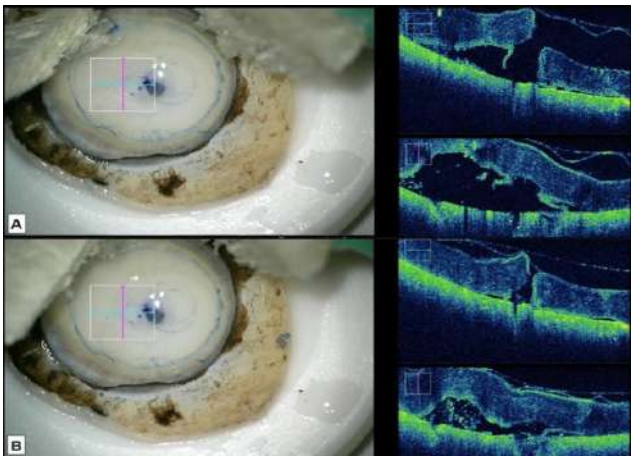
Residual interface space between the DSAEK graft and the host cornea

DMEK

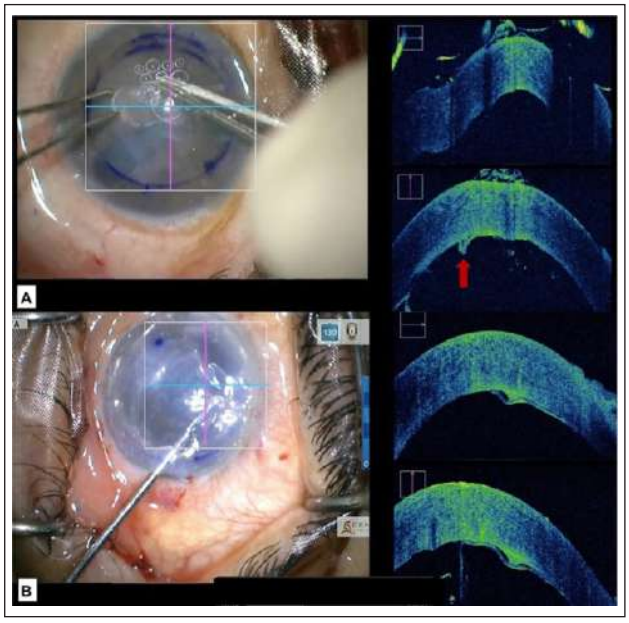
MiOCT imaging helps in each surgical step of DMEK surgery. This influences the decision-making which eventually leads to high success rate.

MiOCT aids the surgeon in visualization of complete removal of the Descemet's membrane in the recipient even in opaque corneas. Also, any remnant DM tags, fibrosed DM can be easily visualized[18,19]. MiOCT allows direct visualization of unfolding and orientation of the DMEK graft in anterior chamber. This advantage of MiOCT is very much essential especially in severe corneal oedema cases thus helping in visualization of structures beyond cornea[2].

After attaching the DMEK graft with an air bubble, the apposition of graft to stroma and possible detachments or folds, can be easily seen with MiOCT[18].



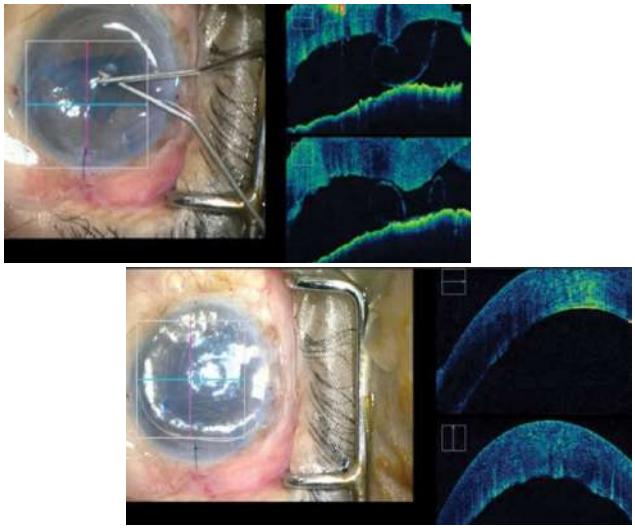
Intraoperative images of donor tissue preparation before trephining the peeled graft **(A)** showing fluid between the peeled DMEK graft and stromal bed on Mi-OCT; **(B)** showing the decrease in fluid space with the peeled DMEK graft falling back on the stromal bed after drying the edges with a Merocel wick on Mi-OCT.



Intraoperative images (**A**) showing retained DM tag (marked with red arrow) after descemetorhexis; (**B**) removal of a retained DM tag with intravitreal forceps.

PDEK- Pre Descemets endothelial keratoplasty

PDEK involves the separation of the pre- Descemets layer (PDL) and the DM-endothelium complex from the residual donor stroma by the formation of a Type 1 big bubble.



Bowman layer transplantation

Bowman layer (BL) transplantation is a relatively new surgical procedure for treatment of advanced keratoconus in corneas that are too thin or steep for intracorneal ring segment implantation or ultraviolet cross-linking. An isolated, donor BL is inserted into a manually dissected, mid-stromal pocket to serve as a mechanical splint, flattening the recipient cornea by approximately 8–9 diopters (D). C Maya Tong et al in their study of 21 consecutive eyes of 21 patients (16 male, mean age 30 ± 12(SD) years (range 19 to

64 years) underwent MiOCT assisted BL transplantation. In 2 eyes, intraoperative perforation during stromal dissection resulted in the operation being aborted. In the remaining 19 eyes, BL transplantation was successfully completed. Mean thinnest point corneal thickness measured 380 (±43) μm preoperatively, 423 (±87) μm 1 day postoperatively, 389 (±63) μm 1 month postoperatively, and 379 (±52) μm at 6 months postoperatively. 89% of patients (16/18) demonstrated a reduction in Kmax 1 day postoperatively, which was maintained in 86% of patients (12/14) at 6 months postoperatively.

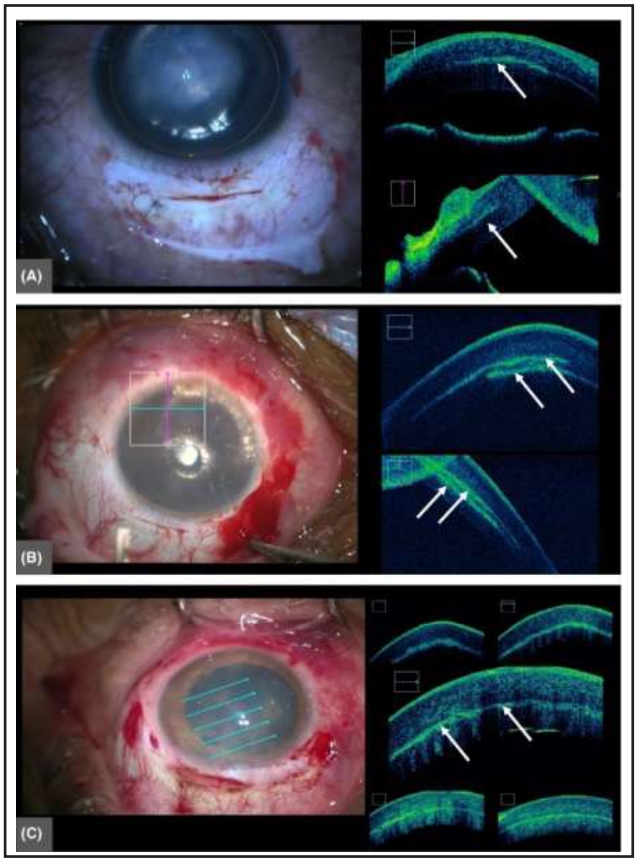


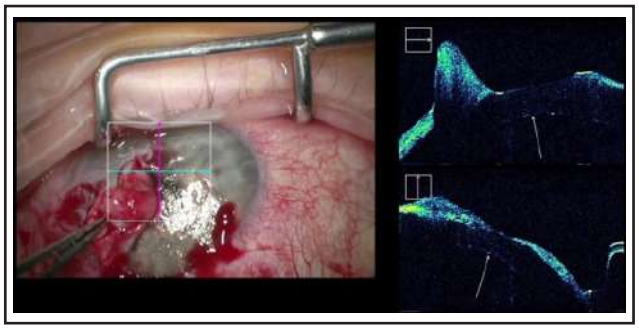
Figure - Intraoperative OCT (iOCT) revealing the plane of ongoing stromal dissection, even when the surgeon's direct view is obscured by stromal scarring (A). This enhanced visualization may also permit the detection of multiple (mistaken) dissection planes (B), and confirmation of graft placement (C).

Corneal Tattooing

Agarwal et al well documented the use of MiOCT in intrastromal keratopigmentation. This study was conducted to know the surgical experience of novice ophthalmic residents in using MiOCT for corneal tattooing. MiOCT helped surgeons in guiding the desired depth of dissection during lamellar dissection and also the end point of tattooing noted by the shadowing effect of ink on underlying structures[20].

Other corneal lamellar procedures

MiOCT can also be used during corneal patch grafts, dermoid excision with lamellar keratoplasty.



Evaluation of preparation depth during corneal pannus removal to avoid penetration of the globe as the remaining corneal thickness cannot be seen through the surgical microscope (arrows points at the posterior cornea)

Limitations of MiOCT

1) The equipment is costly.

2) Machine induced shadowing which makes the structures beyond the metallic instruments' invisible. Thus, affecting the stromal layer dissection difficult some times.[21]

Conclusion

MiOCT is a valuable tool and guide in the field of ophthalmology as it guides the surgeon in decision making and directly influence the success rate of surgery.

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Pediatric Glaucoma: Diagnosis, Management, Treatment

- Dr. Isabella V. Wagner, [1] Dr. Christian Draper, [1]
Dr. Leticia Checo, [1] Dr. Derya Simsek,[2] Dr. Syril Dorairaj [1]
[1] Department of Ophthalmology, Mayo Clinic, Jacksonville, FL
[2] Baskent University Medical School, Ankara, Turkey

Introduction

Glaucoma is a rare but serious cause of childhood blindness around the world, affecting 1.2% of children in Great Britain, 3% of children in northern India and up to 7% of children in southern India.[1-3] Pediatric glaucoma requires coordinated lifelong care from an early age between the patient, provider, and caregiver which aside from significant morbidity carries other difficult to measure daily burdens such as cost and quality of life.

Primary congenital glaucoma (PCG), the most common form of primary childhood glaucoma, accounts for 5% of childhood blindness worldwide.[4] In developed countries such as the United States, Great Britain, Ireland, and Australia, the incidence of PCG ranges from 1 in 10,000 to 30,000 live births but this can be variable dependent on ethnicity.[5-7] Ethnic groups with high prevalence of consanguinity have the highest reported incidences, particularly Pakistani children with an almost 9x greater risk than Caucasian children to develop PCG.[8] The estimated incidence in Saudi Arabia is 1 in 2500 while the highest reported incidence worldwide is in Slovakian Gypsies at 1 in 1250 live birth.[9] PCG is consistently reported more commonly in males in the United States and Europe with a male to female ratio of 3 to 2.[10-12]

The other primary childhood glaucoma, juvenile open-angle glaucoma (JOAG) is estimated to comprise 2% to 4% of all childhood glaucomas while secondary forms are more common, accounting for 40% to 45% of childhood glaucoma.[13]

According to the World Glaucoma Association (WGA), pediatric glaucoma comprises all disorders with elevated intraocular pressure (IOP)-related damage to the eye in childhood. Unlike adult glaucoma, this definition is not solely based on optic nerve appearance or visual field defects which can be difficult to ascertain in children. Many classification schemes have been used to organize pediatric glaucomas but consensus in the 2013 WGA meeting organizes pediatric glaucomas as primary or secondary. The primary forms, as previously mentioned, include PCG and JOAG. Secondary forms can be acquired from trauma, uveitis, steroid use, tumor, retinopathy of prematurity, or after cataract surgery. Secondary nonacquired forms can include those associated with systemic conditions such as chromosomal disorders, phakomatoses, or those associated with ocular abnormalities such as Axenfeld-Rieger, aniridia, peters anomaly, and iridotrabecular dysgenesis [14]

While the WGA discourages the use of words with inconsistent definitions such as developmental, congenital, or infantile, PCG is frequently broken down by age of presentation to: (1) newborn onset (0 to 1 mo), (2) infantile onset (1 to 24 mo), (3) late onset or late recognized (>24 mo), and (4) spontaneously arrested cases. Spontaneously arrested cases are rare but represent cases with normal IOP and optic discs but with other typical signs of PCG that are not progressive. Timing of diagnosis may be different in areas with variable health care access and is influenced by severity of disease. While PCG will commonly present between 3 and 9 months of age, newborn onset is the most severe.[15]

Table 1 Classification of Pediatric Glaucoma

Primary glaucoma	Primary congenital glaucoma		
	Juvenile open angle glaucoma		
Secondary glaucoma	Glaucoma following cataract surgery		
	Nonacquired systemic disease	Congenital idiopathic cataract	
		Congenital cataract associated with systemic syndrome or ocular anomalies	
		Acquired cataract	
		Chromosomal disorders	Trisomy 21
		Connective tissue disorders	Marfan syndrome
			Weill-Marchesani syndrome
			Stickler syndrome
		Metabolic disorders	Homocystinuria
			Lowe syndrome
			Mucopolysaccharidoses
		Phacomatoses	Neurofibromatosis
			Sturge-Weber syndrome
	Nonacquired ocular anomalies	Rubinstein-Taybi	
		Congenital rubella	
		Aniridia	
		Axenfeld-Rieger spectrum	
		Congenital ectropion uveae	
		Iris hypoplasia	
		Oculodermal melanocystosis	
		Peters anomaly	
		Persistent fetal vasculature (before cataract surgery)	
		Posterior polymorphous dystrophy	
		Ectopia lentis	
	Acquired conditions	Postsurgical (not cataract surgery)	
		Retinopathy of prematurity	
		Steroid induced	
		Trauma	
		Tumors	
		Uveitis	

Etiology and Pathogenesis

PCG is most often sporadic, however, there are autosomal recessive cases with penetrance ranging from 40% to 100%.[16] Linkage analysis have thus far identified 5 loci that are involved with the development of PCG: GLC3A (located on chromosome 2p22-p21), GLC3B (1p36.2-p36.1), GLC3C (14q24.3), GLC3D (14q24.2-q24.3, not overlapping with GLC3C), and GLC3E (9p21) (16,18). Genes have been identified with 3 of the 5 loci. The GLC3a loci contains the CYP1B1 gene, the GLC3D locus contains latent transforming growth factor beta binding protein 2 (LTBP2) and the GLC3E loci contains tunica internal endothelial cell kinase gene (TEK/TIE2).[15] CYP1B1 mutations are associated with 15% to 20% of PCG cases in Japan and the United States and LTBP2 mutations have been reported in consanguineous Iranian, Pakistani, and Slovakian Roma families.[4,17-19] Genetic testing can identify a cause in 40% of cases of PCG; in cases of parental consanguinity, it is essential to screen current and future siblings.[4]

The exact mechanism by which the genes cause PCG has yet to be understood, but the final common pathway seems to affect anterior chamber development which results in poor aqueous outflow secondary to abnormal development of the aqueous drainage system. Anderson [20] found PCG patients to have thicker collagenous beams within the trabecular meshwork, anterior iris root, and ciliary body insertion which obstructs the trabecular meshwork or compresses Schlemm canal.

JOAG is most commonly diagnosed in individuals between the ages of 5 to 35 years [21,22] and is considered of a subset of primary open-angle glaucoma. In contrast with PCG, JOAG is in some cases inherited in an autosomal dominant manner with high penetrance.[22] The most important gene in association with the pathogenesis of JOAG is the gene myocilin. It can be found at the GLC1A locus at 1q23-25. Mutations in this gene account for up to 36% of affected individuals.[23] Myocilin can also be involved with PCG but to a lesser extent. Mutations in myocilin are thought to increase the resistance to aqueous outflow as it expresses a protein on the trabecular meshwork.[24, 25]

Diagnosis

In addition to a thorough routine medical history, caregivers should be asked if infant demonstrates tearing, eye rubbing, irritability, or hiding covering their eyes especially when taken outside into sunshine or in light. Observations from the caregiver on corneal clouding, blue tint, or buphthalmos (ox-eye) may be helpful as well. Older children may be referred due to failed vision screenings, trouble seeing in classroom, or eye pain.

The physical examination should encompass the standard ophthalmology exam for infants and young children but should be focused on efficiency, especially in measurement of IOP which should be measured before instillation of dilating drops and when child is calm. IOP can be reliably measured with many instruments such as the Perkins tonometer, tonopen, Icare rebound tonometer or Goldmann applanation in older and more cooperative children. Of note, Icare rebound tonometry readings may overestimate IOP compared with Perkins tonometry and underestimate IOP in edematous corneas compared with the tonopen.[26] If patient cooperation precludes accurate IOP measurement, exam under anesthesia (EUA) should be performed. Most anesthetic agents lower IOP except for chloral hydrate and midazolam which have no effect on IOP and ketamine which can raise IOP.[27-29] Thus, IOP measurements should be obtained soon after induction and before intubation. Normal IOP of newborn is in the low teens and increases to normal adult levels by 7 or 8 years of age.[15]

Elevated IOP in the pediatric population manifests with many ocular findings. The cornea and sclera may stretch until 3 years of age leading to enlarged corneal diameter, increased anterior chamber depth, and increased axial length. Ocular stretching can be commonly seen in all forms of glaucoma in early childhood (Fig. 1). A normal newborn's corneal diameter is 9.5 to 10.5 mm and increases to 11 to 12 mm by 1 year of age which can be measured more easily horizontally but also vertically with calipers. Occasionally, the corneal diameter can be estimated with a photograph of ruler in picture for scale.[30] High IOP causes endothelial dysfunction leading to corneal edema, opacification, and breaks in Descemets membrane. These breaks in Descemet membrane are termed Haab striae which can be seen even after IOP is normalized and is histologically evident as areas of bare corneal stroma with surrounding hyaline deposition on the broken Descemets and endothelial edges (Figs. 2, 3).

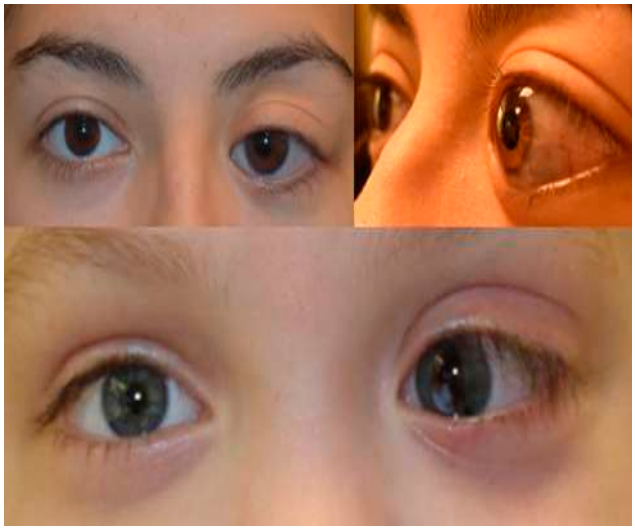

Figure 1. These children demonstrate buphthalmic left eyes and normal right eyes. The girl in the bottom panel has a left eye axial length of 27.39 mm.

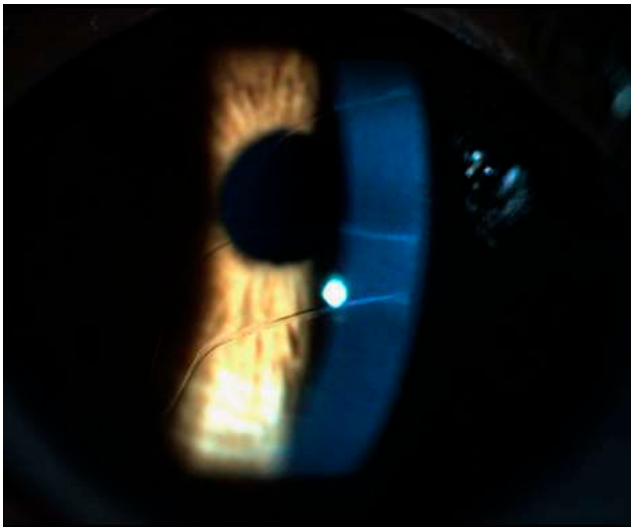

Figure 2. Haab striae. These hyalinized breaks in endothelium will persist after corneal edema has resolved.

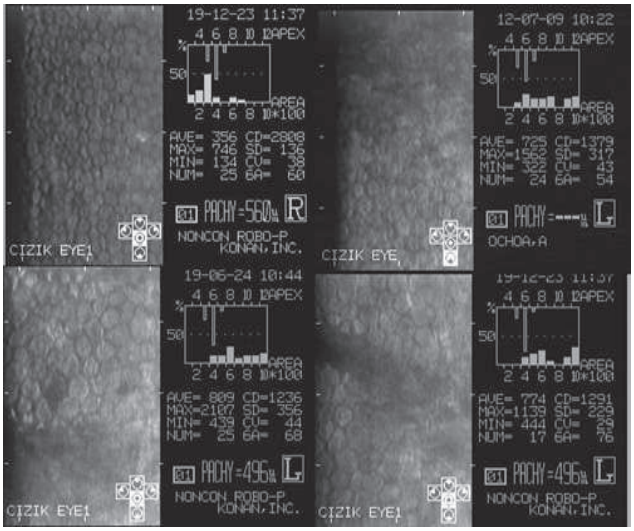

Figure 3. Specular microscopy in a single patient with normal right eye (top left) and buphthalmic left eye. Decreased endothelial cell count and variable cell morphology can be seen as well as areas of missing endothelial cell corresponding to Haab striae.

The role of pachymetry in PCG and secondary forms is uncertain but may be helpful in JOAG. Full term newborn eye has a mean axial length of 16 to 18 mm.[31] Cycloplegic retinoscopy can detect axial myopia, anisometropia, or corneal irregularity which is seen due to abnormal ocular stretching of the anterior and/or posterior segment. Optic nerve cupping may result without loss of rim tissue from posterior bowing of the lamina cribosa. When IOP is normalized, this reversal of cupping may occur as pediatric sclera is more elastic than adults. The normal newborn has a small physiological cup, typically <0.3 cup-to-disc ratio.[32]

Gonioscopy is commonly performed under anesthesia for initial diagnosis. It can be done in clinic if tolerated using an indirect gonioscopy lens that fits between a child's small palpebral fissure. The gonioscopy is used to help guide surgical planning in cases of PCG, but can also be used to identify other angle abnormalities which point to a secondary cause of glaucoma such as posterior embryotoxon and prominent iridocorneal adhesions found in Axenfeld-Rieger anomaly.[15] Children with PCG may have scalloped edges of the peripheral iris and pale glistening peripheral iris stroma appearance, but do not have a visible scleral spur due to the peripheral iris inserting into the trabecular meshwork.[15] In JOAG, the angle takes on a normal appearance and gonioscopy can typically be performed in cooperative older children.

Anterior segment optical coherence tomography and ultrasound biomicroscopy may also demonstrate abnormal anterior segments particularly in patients with secondary glaucoma or associated syndromes (Figs. 4, 5).

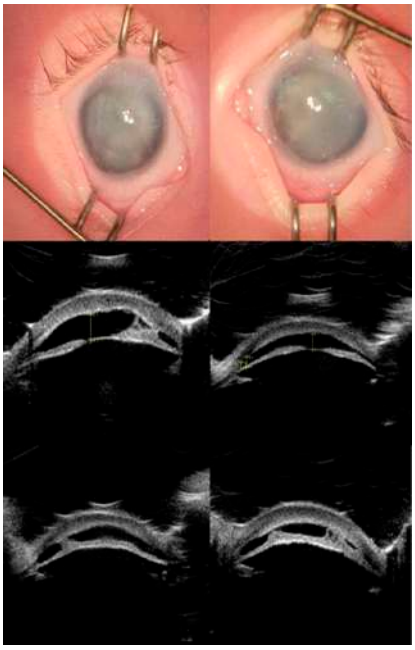

Figure 4. Ultrasound biomicroscopy may also be helpful to evaluate the anterior chamber structures. This preterm infant had elevated intraocular pressure and cloudy cornea precluding evaluation of the anterior chamber. Iridocorneal adhesions can be seen and an anterior chamber depth of ~1 mm was measured.

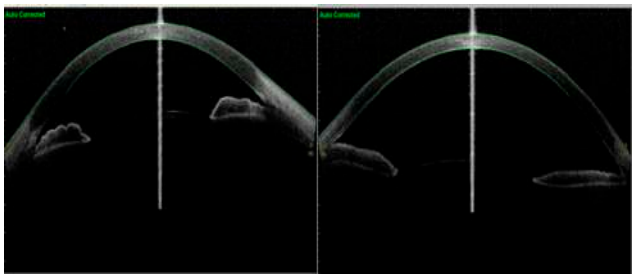

Figure 5.AS Anterior segment OCT of a patient with normal right eye (right) and primary congenital glaucoma (PCG) left eye after trabeculotomy (left). A flattened iris with reduced folds is seen in up to 60% of patients with PCG.[33] Other abnormalities such as a high iris insertion or absence of schlemm canal may be variably demonstrated on ASOCT. ASOCT indicates anterior segment optical coherence tomography. This patient also had severe endothelial cell loss in the left eye compared with right.

Management

The management of pediatric glaucoma is directed toward IOP lowering as well as managing the secondary complications such as amblyopia, refractive changes, corneal clouding, and buphthalmos. Blindness is most often from amblyopia rather than loss of optic nerve tissue.

Although surgical management is the mainstay of management of PCG and is required in most JOAG patients,[34] medications serve as useful primary adjuncts and can be notably effective for secondary forms of glaucoma such as aphakic, uveitic, or steroid glaucoma. However, the optimal therapeutic modality must be individualized and depends on age, degree of glaucomatous optic neuropathy, associated ocular features, and health of the child.

Medical Management

Beta adrenergic antagonists decrease aqueous production in the ciliary body. Medication types include timolol (nonselective beta-1 and beta-2 blocker, concentrations of 0.25%, 0.5% solutions and 0.25% and 0.5% gel-forming) and betaxolol (selective beta-1 blocker, concentrations of 0.25% and 0.5% solutions). Beta blockers typically reduce the IOP by 20% to 30% in adults.[15] Plasma timolol levels in children after using 0.25% greatly exceed the levels in adults using 0.5% concentration potentially increasing the risk of side effects such as bronchospasm and bradycardia [35] and even severe fatigue. Therefore, betaxolol and timolol gel 0.25% have been used as an alternative to 0.5% due to less systemic absorption and can be used once daily.[36]

Carbonic anhydrase inhibitors can be administered orally (acetazolamide and methazolamide) or topically (dorzolamide and brinzolamide). Dorzolamide was found to be well tolerated and effective for at least 3 months in children younger than 6 years of age.[37] Both oral and topical carbonic anhydrase inhibitors have been found to significantly reduce the IOP, however, topical dorzolamide is less effective in comparison to acetazolamide (27% vs. 36%).[38] Side effects can occur in >40% of patients taking oral carbonic anhydrase inhibitors, including lethargy, diarrhea, metabolic acidosis, decreased appetite, and GI discomfort.[15] Topical carbonic anhydrase inhibitors should be used later in the treatment algorithm if corneal endothelial function is compromised.[16]

Prostaglandin analogs may decrease IOP through increased uveoscleral outflow. Examples include latanoprost, travoprost, bimatoprost, and tafluprost. Latanoprost reduces IOP in PCG by 15% to 20%.[39] Side effects include eyelash growth, conjunctival injection, iris pigmentation, and periocular hyperpigmentation.[15] Another known side effect is orbital fat atrophy which may be beneficial in buphthalmic children as the proptotic appearance may be lessened. Long-term effects have not been studied in children. Prostaglandin analogs use in children is not approved by the United States Food and Drug Administration, but latanoprost is approved for children in Europe.[15]

[alpha]-adrenergic agonists decrease aqueous production and increase uveoscleral outflow and include apraclonidine and brimonidine. Brimonidine is a lipophilic drug which can cross the blood-brain barrier causing central nervous system depression, apnea, hypotonia, hypothermia, bradycardia, hypotension, somnolence, and even coma.[15] It is contraindicated in children younger than 2 years of age [15] and to be used with caution in children between ages 3 and 10 years. Apraclonidine is a hydrophilic drug and thus better tolerated but is more useful for short-term IOP control in children planned for angle surgery due to tachyphylaxis and a very high allergy rate.[15,40]

Other medications include combination beta-blocker/carbonic anhydrase inhibitor and miotic agents. A combination beta-blocker/carbonic anhydrase inhibitor such as timolol 0.5%-dorzolamide 2% has been shown to be effective in reducing IOP in children requiring more than one topical medication.[15] Miotic agents can be used perioperatively for angle surgery, but due to immature angle anatomy and high ciliary muscle insertion are not useful in the treatment of PCG.[15] Rho Kinase inhibitors and latanoprostene bunod have had limited clinical use in children to date.

Surgical Therapy

In PCG, the initial procedure of choice is angle surgery via goniotomy or trabeculotomy to open the trabecular meshwork and allow aqueous flow from the anterior chamber directly into the canal of Schlemm. The overall success rates of angle surgery is reported to range from 72% to 100%, and is most successful when performed between 1 and 12 months of age; however, there is still a 15% to 20% chance of failure with angle surgery.[41] The success rate of angle surgery is much lower in children born with glaucoma than in those diagnosed between 3 months and 2 years.[42] Some surgeons elect to perform the first stage of a tube shunt during trabeculotomy in these high risk eyes given the high potential of needing additional surgery.

When the cornea is hazy and precludes good visualization, an ab externo trabeculotomy is preferred.[41] The traditional technique for a trabeculotomy uses an external access to the canal of Schlemm via a partial scleral flap. A trabeculotome opens 90 degrees of the canal which can then be rotated into the anterior chamber to incise through the trabecular meshwork. A trabeculotome in the opposite direction will open the canal an additional 90 degrees to create maximally a 180 degree trabeculotomy. A 360 degree trabeculotomy treatment can maximize the IOP lowering potential; a 6-0 polypropylene suture or an illuminated microcatheter can be threaded through the entire canal of Schlemm and pulled across the anterior chamber to complete the 360 degrees in 1 session through 1 incision.

Goniotomy can be performed under direct visualization

of the nasal angle by creating an incision across the trabecular meshwork with a goniotomy knife or modified devices such as Kahook dual blade or trabectome. Ab interno trabeculotomy which is similar to goniotomy can also be performed with gonioscopy-assisted transluminal trabeculotomy or Omni (Sight Sciences).

In a comparison between circumferential trabeculotomy with an illuminated microcatheter versus standard goniotomy for treatment of PCG, microcatheter-assisted had a 91.6% qualified success rate compared with 53.8% qualified success rate with conventional goniotomy at 12 months.[43] In addition, 360 degree trabeculotomy showed a success rate of 85.7% compared with a success rate of 58.4% with traditional trabeculotomy at 12 months follow-up.[44] Angle procedures have also been reported to be safe and effective in JOAG patients and can be considered in open angle aphakic glaucoma and open angle glaucoma associated with aniridia.[45-48]

When angle surgeries and medical management have failed, filtering surgery is considered the next line of treatment, including trabeculectomy with mitomycin C (MMC) and glaucoma drainage device implantation. The success rate of trabeculectomy with or without antimetabolites in patients younger than 20 years of age ranges from 55% to 92%. This success rate is notably worse in aphakic patients and children younger than 1 year of age due to the high inflammatory response leading to scarring.[49] While antimetabolites are useful in prevention, a retrospective analysis of 44 JOAG patient demonstrated increased risk of hypotony maculopathy and bleb related infection with MMC use without increased probability of success.[50] Furthermore, pediatric cases of trabeculectomy with MMC can exhibit an increased incidence of bleb leak, blebitis, and endophthalmitis. Bleb related infection has been reported in up to 17% and endophthalmitis has been reported up to 9% of pediatric patients with MMC trabeculectomies.[42] Children who undergo trabeculectomy would have permanent lifestyle restrictions that are often difficult to maintain such as avoidance of strenuous activity and meticulous hygiene. Caregivers should be aware of detecting signs of infection

Studies in the Middle East suggest that combined trabeculotomy-trabeculectomy delivers better IOP control and vision preservation in patients with severe PCG with corneal opacity.[51] From a limbal based flap, a partial thickness scleral trapdoor is made up to the limbus and an incision into schlemms canal is used to introduce the trabeculotome for a maximum 180 degree trabeculotomy. Under the same scleral flap, but a site different from the incision into the canal, the trabeculectomy can be performed routinely. These studies demonstrate 93.5% success rate with combined procedure compared with 72% primary trabeculectomy after 2 years follow-up.[51]

An additional option for filtering surgery is a glaucoma drainage device which is useful in children since it does not require lifestyle modification. In addition, it is useful in those with significant conjunctival scarring or aphakia due to increased risk of infection with contact lenses in the setting of a prior trabeculectomy. Glaucoma drainage devices provide the advantage of the ability to lower IOP even after failed trabeculectomy and can survive future surgeries for concurrent intraocular conditions.[41] Success rate for pediatric patients younger than 18 have ranged from 31.3% to 97.2% with variable follow-up.[42] At 5 years, patients with a double plate Molteno or Baerveldt have a 67% success rate and for Ahmed valve, success is reported at 55%.[15,52] Notably, children are also more likely to require topical medical therapy after tube surgery with qualified rates up to 85.8%.[52] Endophthalmitis is reported at a 5 times higher rate compared with adults [53] and is more common with inferior tube shunts possible due to maxillary sinus infections which are common in children. Anterior tube migration is expected in PCG patients due to thin sclera and growth of the eye. In addition placement of a tube shunt is more technically challenging due to the stretched sclera in buphthalmos and higher risk of scleral perforation.

Cyclodestructive procedures have typically only been used in children with refractory glaucoma or who have failed angle and filtering surgery to reduce aqueous production. Often multiple treatments are necessary to achieve the desired long-term IOP lowering effect due to the regenerating ability of the ciliary body epithelium and the excess aqueous production capacity.[41] Previously, cyclocryotherapy was the preferred method, but this has been largely replaced with laser cyclophotocoagulation using a diode laser. Transcleral and endoscopic application of the laser are both options with an endoscopic approach helpful in eyes that are aphakic and or have abnormal anatomically. Success has been unpredictable. With transscleral application, the success rate ranges from 30% to 79% with retreatment in about 70% of patients.[54-57] Using endoscopic application, the success rate has been reported 64% at 1 year and 16% by 5 years. Endoscopic retreatment brings the success rate up to 81% at 1 year and 34% at 5 years.[58,59] Complications may include hypotony, retinal detachment, visual loss, and phthisis.

Newer options for surgical treatment of pediatric glaucoma include nonpenetrating glaucoma surgery (viscocanalostomy and deep sclerectomy) and minimally invasive glaucoma surgeries (MIGS). These surgeries attempt to lower the IOP and minimize the complications associated with penetrating surgeries. Viscocanalostomy has demonstrated success rates up to 89% at 20 months.[60] A single deep sclerectomy procedure has a reported success rate of 58%[42] but can be complicated by poor identification of Schlemm's canal. "MIGS" devices such as the Hydrus (Ivantis Inc., Irvine, CA), Istent (Glaukos Corporation, San Clemente, CA), PreserFlo (Santen Inc., Miami, FL; formerly known as the InnFocus MicroShunt), and Xen gel stent (AqueSys Inc., an Allergan affiliate, Aliso Viejo, CA) have not been evaluated in children.

Prognosis/Follow-up

Visual prognosis ultimately depends on age of diagnosis and onset combined with severity of disease with amblyopia causing the majority of vision loss. Despite aggressive and successful IOP control, vision loss mostly due to amblyopia, may still occur due to a combination of refractive amblyopia and deprivational amblyopia. A study at the Children's Hospital of Philadelphia reviewed a total of 133 eyes with varying types of pediatric glaucoma and found that at least 60% of patients had vision >=20/200 and 46.6% of patients had good visual acuity of >=20/70. Diagnosis of PCG conferred the best visual prognosis with vision of >=20/70 in 69.4% of patients.[61] These patients require lifelong follow-up but the burden of follow-up is most profound within the first 4 years of diagnosis. One study evaluating 60 patients with pediatric glaucoma found the total combined interventions including EUA, glaucoma surgeries, emergency department visits to be 9.9, 5.7, 4.6, and 4.8 at years 1 to 4, respectively, indicating the high burden of disease on the patient and family within the first few years of life.[62]

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Variations of scleral flap sutures in trabeculectomy surgery

Dr. Aditi Singh [1], Dr. Unnikrishnan Nair [2]

[1]Glaucoma and Cataract Services, Chaithanya Eye Hospital and Research Institute, Trivandrum, Kerala, India; [2]Vitreoretinal Services, Chaithanya Eye Hospital and Research Institute; Department of Research, Chaithanya Innovation in Technology and Eyecare (Research), Trivandrum, Kerala, India

Corresponding Author: Dr. Aditi Singh: adittisingh@gmail.com

Introduction:

More than half a century has passed since the introduction of Sugar/ Cairns / Watson filtration procedure of trabeculectomy and it still remains the gold standard surgical procedure for medically uncontrolled glaucoma till date .[1,2]

Trabeculectomy, however comes with its own sets of complications such as postoperative over filtration, sight threatening hypotony, shallow or flat anterior chamber, choroidal detachment, aqueous misdirection syndrome, suprachoroidal haemorrhage to name a few.[3,4,5]

A meticulously constructed scleral flap is of utmost importance to achieve adequate drainage as it serves as the primary resistance to aqueous outflow in the early postoperative period.[6,7]To achieve the desired outflow and target intra ocular pressure, suture adjustments and bleb interventions are frequently necessary in the post operative period. [8,9] Additionally the use of antimetabolites calls for a meticulous suturing of the scleral flap and conjunctiva.[10]

Various techniques have been described in literature pertaining to shape, size and construction of scleral flap, appropriate use of anti metabolite agents and suturing modalities. During trabeculectomy, the scleral flap sutures should be loose enough to permit aqueous humor outflow but tight enough to prevent postoperative hypotony, anterior chamber shallowing, and choroidal detachment. Different sutures such as lysable, releasable sutures and adjustable sutures are being used to modulate filtration and achieve desired results.[11-20]

The aim of this article is to describe various types of scleral flap suturing techniques used in trabeculectomy surgery.

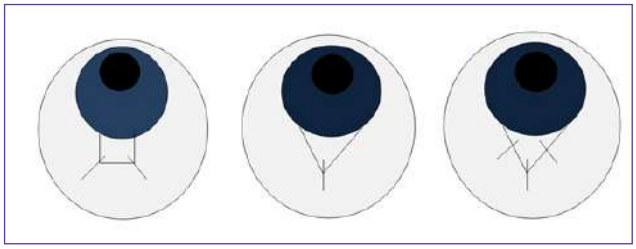
Hoskins and Migliazzo in 1984, introduced the idea of cutting “permanent” sutures with a laser, allowing the scleral flap to open.[21]The use of releasable sutures in trabeculectomy surgery was first mentioned by Schaffer in 1971 where externalised mattress sutures were used to prevent shallow AC following thermal sclerostomies.[22]The method described by Cohen and Osher with a trimmed suture end on peripheral cornea, remained the most popular.[23]

Lysable Sutures in Standard Trabeculectomy Surgery:

Suturing the Trabeculectomy Flap:

Suturing the flap may be performed in different manners. A standard 3-1-1 knot, 3-2-1 knot or a slipknot may be used at the apices of a rectangular trabeculectomy flap(Fig 1 a) , apex of triangular sclera flap (Fig 1 b) and on both the sides of the triangular flap as well depending upon the indication and need. (Fig1 c)

Suturing the trabeculectomy flap requires first passing a half-thickness scleral bite at each apex of the flap with a 10-0 nylon suture. Colibri forceps may be used to grasp the flap and stabilize the tissue as the needle is passed through the flap. Care should be taken so as not to tear the flap or create a button hole in it.



The goal of suture placement and tying is to allow the flap to sit in its dissected scleral bed, without distortion of the wound edges. Each suture should be placed symmetrically and equidistant from each corner of the flap. The anterior chamber should be filled with balanced salt solution prior to suturing so as to achieve a normal physiological intra ocular pressure. Tying sutures on a trabeculectomy flap in a hypotonus eye may eventually cause the suture tension to be too tight. This may result in a trabeculectomy flap that prohibits adequate filtration from the trabeculectomy site.

The flap should be sutured at each corner, with equal tension to allow adequate flow of aqueous from under the flap. Using straight tying forceps to grasp one end of the suture, three loops of suture are thrown over the curved tying forceps. The curved tying forceps are then used to pull the trailing end of suture through the triple loop. This first throw of suture should then be pulled to the appropriate tension, positioning the trabeculectomy flap so the knot lies flush against the sclera. To place the second throw, the straight tying forceps are used to throw one loop over the curved tying forceps, and the knot is pulled in the opposite direction of the first triple-thrown suture pass. The second throw will determine the final tension of the suture knot, and should be thrown taking care not to disrupt the tension of the first triple-thrown suture or to lift the first triple-thrown suture off the sclera and thereby loosen the tension. The third throw of the suture is placed in the same manner as the second throw but pulled in the opposite direction to form a square knot and lock the suture knot in place.[24]Once the sutures are placed, the anterior chamber is reformed and outflow of aqueous is tested with balanced salt solution through the paracentesis.

The suture knot should be buried inside sclera so that it will not have any suture knot–related conjunctival perforation or foreign body sensation.

Pre- placing the scleral flap sutures is technically easier on a firm globe before intraocular entry, and the sutures can be tied rapidly during closure to shorten the duration of intra operative hypotony.[11]

Samsudin et al[25] showed that with a higher number of sutures, the pressure drop becomes smaller. With well-constrained flaps, there is less space and aqueous humor flow underneath it. Less aqueous humor escapes through the flap gap and thus a higher pressure is maintained.

Laser Suture Lysis :

If the need arises laser suturelysis can be done at a later date to achieve the desired intra ocular pressure. Hoskins and Migliazzo first described effective suturelysis when done 1-3 weeks postoperatively.[26-27]

Prior to the use of adjuvants the acceptable window for laser suture lysis in order to achieve a favourable outcome was within the first 2 weeks (day 4 to 3 weeks window period) postoperatively.

However with the intraoperative use of Mitomycin C which causes delayed wound healing, there has been an extended “window period” to perform laser suturelysis. [28-29]

Common lenses used for laser suture lysis are – Hoskins, Blumenthal, Ritch, Layden, Mandelkorn and Wells. [30]Argon laser (514nm) is the most common laser used for laser suture lysis, universally. However, the other lasers that can be used are Nd: YAG (1064 nm or 532 nm frequency-doubled) Diode laser (840 nm), Krypton (647 nm) and Yellow Pascal(577 nm).

Hand held laser suture lysis contact lens is gently pressed over the conjunctiva focusing on the suture to be lysed in a topically anesthetised eye. Pressure of the lens blanches the conjunctiva thus helping focus the suture adequately, stabilizes the globe and focuses the laser energy , which is delivered by the laser aiming beam around 50 microns in size.

Laser suture lysis is a simple technique which can be performed as an outpatient procedure without a steep learning curve and prolonged surgical time.

Complications following laser suture lysis have been noted in around 30% of the cases[31] the most common being hypotony. Immediate complications can be wound dehiscence and conjunctival perforation. Early complications can be hypotony, flat / shallow anterior chamber , iris incarceration , malignant glaucoma, hyphema and late complications can be progressive lenticular opacity and larger filtering blebs leading to corneal dellen.[32-36]

Releasable suture:

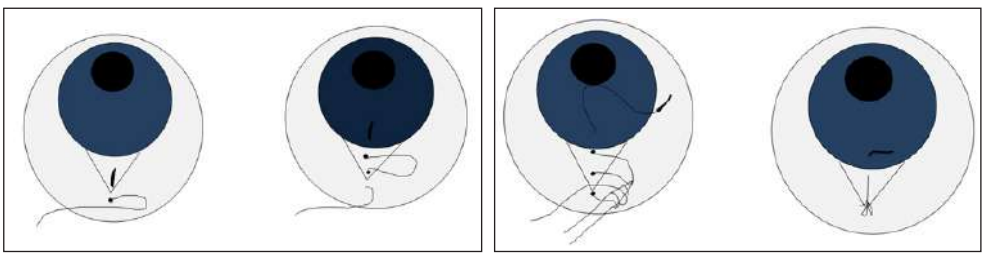
Various techniques for releasable sutures have been described in literature such as Wilson’s, Shin’s, Cohen’s, Kolker’s and Johnstone’s.

The releasable suture may be removed using jeweller’s forceps on the slit lamp at a later date depending upon the need. A releasable suture is ideal in eyes where difficulty in finding the sutures postoperatively is expected, such as eyes with heavily pigmented conjunctiva, thick Tenon’s tissue, or a large amount of subconjunctival haemorrhage intraoperatively[37] or where the benefit of laser suturelysis not available.

In this article we will be describing Cohen`s - Osher`s [23] and Kolker`s technique[38].

Cohen`s and Osher`s Technique :

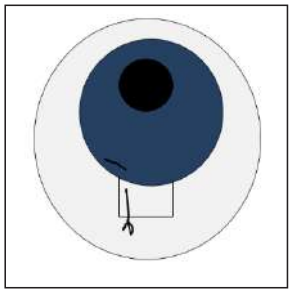
(Fig2 a,b,c,d) Suture bite is taken through the intact sclera to the apex of a triangular scleral flap .Next the suture is passed through the centre of the base of the triangular scleral flap to the clear cornea .A four throw is performed, holding the long tail of the suture with the straight tie in the left hand and throwing four times over the curved tie held in the surgeon’s right hand . Desired tension is achieved and the excess tail of the suture is cut, leaving approximately 2-3 mm of suture resting freely on the cornea



Kolker`s technique :

(Fig3) It is a modification of Cohen's technique.[38] The suture is passed through scleral flap to clear cornea, passing under the limbus. A four throw is performed with the suture, holding the long tail of the suture with the straight tie in the left hand and throwing four times over the curved tie held in the right hand . A slipknot is created, suture is adjusted to the desired tension and the excess tail of suture is cut. The suture is then passed back through clear cornea to clear cornea laterally. End of suture is cut flush to corneal surface, leaving exposed loop but no free end to abrade corneal epithelium.

The releasable suture technique was shown to be an effective and safe method of providing sufficient aqueous humor outflow by easily removing the sutures with forceps.[38-39]



Removal of releasable suture:

Sutures are released with the patient under topical anaesthesia and seated at the slit lamp, by pulling the exteriorized corneal loop with a suture-holding forceps. Sometimes, superficial layers of corneal epithelium may need debridement to pick-up the epithelised suture loop. Intracorneal segment of loop is teased out and pulled with constant, gentle traction to release the loop knot. In cases where suture breaks inadvertently, laser suture lysis can be done.

Complications of releasable sutures include foreign body irritation and keratopathy due to exposed sutures, conjunctival leakage after suture removal, or endophthalmitis caused by externalized sutures that are contaminated with bacteria.[38-39]

Comparison of lysable and releasable sutures :

Matlach et al[40], in their study showed that the results of trabeculectomy using single sutures (lysable sutures) or releasable sutures are equivalent. Their results were based on two comparable groups with a follow-up of 2 years. The data illustrates that both surgical techniques are equally effective, with low complication rates and adequate reduction of intraocular pressure. Therefore, the choice of suture technique should be based on individual patient requirements and surgeon experience.

Similarly study by Aykan et al[41], in which the surgical outcomes of laser suturelysis of single sutures and releasable sutures were compared, revealed no differences in efficacy or complication rates between the groups. They observed an effective IOP reduction in eyes that had suture release both in the early and late postoperative periods after laser suturelysis and suture release.

Alternatively, a comprehensive literature meta-analysis by Zhou et al [42], comparing trabeculectomies performed with and without releasable sutures showed that the two surgical procedures resulted in equivalent efficacy in IOP control, the trabeculectomies performed with releasable sutures were better tolerated than those without releasable sutures. They found that the releasable suture surgical procedure reduced complications such as hypotony, shallow / flat anterior chamber, and choroidal detachment when compared with the traditional practice, with a statistically significant difference in the incidence of hypotony and flat anterior chambers between the two groups.

Simsek et al [43], found that releasable scleral flap sutures reduce the incidence of shallow anterior chamber and iridocorneal touch after trabeculectomy. Releasable scleral flap suture technique and standard trabeculectomy are similar in terms of lowering intraocular pressure at 1-year-follow up.

Adjustable Sutures:

Adjustable suture technique allows transconjunctival adjustment of scleral flap tension post operatively using specially designed forceps with smooth edges (Khaw adjustable forceps Duckworth- and- Kent.com, adjustable suture forceps No. 2- 502). The adjustable suture system allows a gradual titration of IOP – and may allow more control than suture removal or massage .[19,44]

Studies have favoured tying of the scleral flap with adjustable sutures, allowing safer control of intraocular pressure and minimizing the risk of postoperative hypotony[11,45]

Thus, glaucoma surgeons have many suturing techniques in their armamentarium. Choice of appropriate technique depends upon the requirement of the patient and the expertise of the surgeon. Each suturing technique has its own sets of pros and cons and it depends upon the surgeons to bring out the best of each technique in their surgeries.

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Intraoperative Floppy Iris Syndrome and Management of Small Pupils

- Dr. Sunil Ganekal
Davangere Netralaya, Karnataka

Intraoperative floppy iris syndrome (IFIS) is a clinical entity originally described by Chang and Campbell in 2005.[1] This syndrome is known to cause a poor pupillary dilation, intraoperative complications during cataract surgery and is characterized by the following triad of intraoperative signs:

- *Billowing of a flaccid iris stroma in response to ordinary intraocular fluid currents;*
- *Propensity for iris prolapse toward the phaco and/or the side-port incisions;*
- *Progressive pupil constriction.*

A grading system for IFIS[2] was suggested based on the presence of the previously described intraoperative signs as follows:

- **No** IFIS (stable iris without significant miosis)
- **Mild** IFIS (noticeable floppy iris only)
- **Moderate** IFIS (floppy iris and miosis)
- **Severe** IFIS (floppy iris, significant miosis and strong tendency to iris prolapse).

Two additional pupil features may be present in IFIS:

- Poor preoperative pupil dilation;
- Elasticity of pupil margin.

In contrast to other causes of small dilated pupil and progressive intraoperative miosis (e.g. diabetes), IFIS is characterized by an elastic iris which does not dilate with mechanical stretching. Therefore, it is important to anticipate IFIS and use pupil expansion devices as a preventive measure in the beginning of surgery rather than after IFIS has developed and the capsulorrhexis is already completed (which might compromise its integrity).[1]

The reported overall prevalence of IFIS in patients undergoing phacoemulsification is variable, ranging from 2% in the Chang and Campbell report in 2005, up to 12.6% in later studies.[3] This wide range of prevalence might be due to the subjective clinical definition of this syndrome and its manifestations being a continuum of severity with variability between patients and between eyes of the same patient.[4] The prevalence also varies among countries and is significantly increased in groups of patients with clinical factors positively correlated with IFIS. Currently in more recent studies, there is a tendency for higher rates of IFIS, perhaps due to the increasingly high prescription rate of medications associated with IFIS and also because of higher awareness and recognition of milder IFIS signs by surgeons.[5]

Pathophysiology

The most likely pathogenic mechanism for IFIS is the antagonism of α1-adrenergic receptors within the dilator muscle of the iris, which prevent the iris from dilation during surgery. This inhibition can happen with the use of some types of medications, such as the most commonly prescribed α1-adrenegic receptor antagonist (α1-ARA) **tamsulosin** used for the management of benign prostatic hyperplasia (BPH). There are 3 subtypes of α1-adrenergic receptors: α1-A, α1-B and α1-D. The subtype α1-A is the main regulator of smooth muscle tone of the urinary system and of iris dilator muscle. α1-B controls blood pressure through arterial smooth muscle relaxation and is highly present in the choroid (a highly vascularized tissue). α1-D contributes for spinal cord innervation and bladder muscle contraction.[1,6] There is evidence that blocking α1 adrenergic receptors results in relaxation of the iris dilator muscle, with poor pupillary tone. Furthermore, it was proposed that the long-term intake of α1-ARA may cause anatomical variations that are permanent and cannot be completely reversed with interruption of medication and is maintained despite the use of preoperative pharmacological dilation with topical cyclopentolate, phenylephrine and ketorolac.[1] A study also reported drug-melanin interaction, which causes iris dilator muscle atrophy and therefore to IFIS.[7]

Risk factors

❖ **α1-Antagonists**

Pharmacological inhibition of α1-ARA reduces the

muscular tone and thus the pressure within prostatic urethra, and it is nowadays the first line medical approach to BPH. With the continuing longer life expectancy, along with the increased diagnosis of BPH in older men, it is expected that patients on α1-ARA treatment requiring cataract surgery will continue to rise. [6,8]

- **Tamsulosin** – is the most commonly prescribed medication for BPH and it is an α1-A subtype selective blocker. In addition to its effects in the prostate, tamsulosin selectively blocks the iris dilator muscle, in which the α1-A receptor subtype predominates. This drug has a half-life of 48-72h [4], and it has been proposed that its constant blockade effect can result in disuse atrophy of the iris dilator muscle and loss of normal smooth muscle tone, explaining why IFIS manifestations may occur even after its discontinuation. Furthermore, smooth muscle tone in iris dilator muscle may be necessary for the overall iris rigidity observed during surgery, suggesting that iris billowing and prolapse in IFIS may be due to loss of the dilator muscle tone.[1] A 2010 study of iris tissue found α1-A receptors in iris arteriolar muscularis, and suggested that tamsulosin-induced dysfunction may include vascular dysfunction of iris vessels. This can lead to loss of vessels' ability to coil, resulting in iris flaccidity and inability to reach normal pupil dilatation.[9] Incidence of IFIS among tamsulosin users was reported to be 37.9-90.0%[1,8], with high odds and relative risk ratios, showing strong positive correlations between tamsulosin use and IFIS (OR 206.5; RR 99.3).[10] Additionally, tamsulosin blocks α1-A receptors with the highest affinity, compared to the other α1-ARAs.
- **Alfuzosin, doxazosin, prazosin and terazosin** – these are non-selective α1-ARAs. They have lower affinity for α1-A and are less associated with IFIS compared to tamsulosin, and therefore are considered a safer choice in cases of expected IFIS undergoing cataract surgery. However, being non-selective blockers, these drugs may have other potential side effects such as postural hypotension. Alfuzosin is considered an alternative to tamsulosin when considering men with BPH requiring cataract surgery, with a 30 times less probable development of IFIS than with tamsulosin.[11]
- **Silodosin** and naftopidil are new selective α1-ARAs with a similar pharmacological profile to tamsulosin. Further studies are needed to characterise the risk of IFIS with the intake of these new uroselective drugs. Some reports state the possible causative role of silodosin in some patients with IFIS.[12]

Other drugs

Some drugs may have a similar effect on the iris and cause some IFIS manifestations, nevertheless its mechanism is not yet fully explained. The incidence and association with IFIS are not as strong as with tamsulosin.[4,6,13] These include: Finasteride, Saw palmetto (Serenoa repens) as a herbal BPH remedy, Angiotensin II receptor inhibitors (e.g. losartan), Benzodiazepines, Donepezil, Duloxetine, Naftopidil and antipsychotics (quetiapine, chlorpromazine, zuclopenthixol, aripiprazole and risperidone).

Gender

It is not yet clear whether gender is a risk factor for IFIS. Most studies report higher frequency and correlation between IFIS and male gender, which may be attributed to the treatment of BPH with α1-ARA. However, α1-ARA are also prescribed in women for urinary retention and hypertension. In addition, female gender has been associated with increased intraoperative complications when compared to male gender, such as posterior capsular rupture, nucleus dropping and vitreous loss. [6,14]

Age

The risk for IFIS may increase with aging due to iris vasculature dysfunction and altered potency of norepinephrine in iris dilator muscles (which is proportional to receptor reserve).[13]

High blood pressure

It remains controversial whether the increased incidence of high blood pressure in IFIS patients is due an independent risk factor (blood pressure) or due to an association with antihypertensive drugs.[6]

Diabetes

The cause is an autonomic neuropathy partially denervating both the sphincter and the dilator muscles.

Surgery (phacoemulsification) duration

Higher mean duration of surgery was found to be associated with IFIS, which might reflect a more difficult procedure in these patients, not necessarily being a risk factor for IFIS.[13]

Diameter of dilated pupil

Regardless of α1-ARA intake, decreased preoperative dilated pupil diameter has been associated with increased risk of IFIS. A dilated pupil with 6.5 mm or smaller is predictive of IFIS in cases of tamsulosin intake.[5]

Several reports found no correlation between the risk of developing IFIS and diabetes mellitus, pseudoexfoliation syndrome, glaucoma, eye colour, coronary heart disease or cerebrovascular disease. [4,6,14,15,16]

Preoperative evaluation and preventive measures

Concerning the clinical features of IFIS, as well as other causes for small pupils, there are several problems during surgery with poor pupil dilation:[17]

- Restriction of the diameter of capsulorrhexis, which increases the risk of pupillary border and capsular

edge trauma with the phaco tip.

- Impaired visualization of the lens and of the capsular bag, as it reduces the intensity of the red reflex.
- Difficult hydrodissection due to peripheral lens and capsular hiding by the iris and difficult removal of subincisional cortex.

Risk assessment and classification systems remain unavailable for IFIS; therefore, it is important to evaluate the patients' preoperative medication history, among with the other possible risk factors (particularly advanced age and small dilated pupil).

Preoperative measures to prevent IFIS include:

- **Discontinuation of medication:** no clear evidence demonstrates that discontinuation of drugs associated with IFIS prior to surgery fully eliminates the risk of intraoperative events nor the severity of IFIS.[18] Tamsulosin has a long half-life and may cause irreversible iris atrophy, hence there is not an apparent benefit in its withdrawal. Chang and Campbell suggested discontinuation of tamsulosin 4-7 days before the surgery, although they stated it does not prevent IFIS completely.[1] Other authors recommend switching to other α1-ARA like alfuzosin which seems to have a better profile regarding the risk of developing IFIS.[19]
- **Pupillary dilation:** instillation of 1% atropine drops qid for 1 week preoperatively is useful in patients taking tamsulosin. Standard measures for preoperative dilation are recommended, which include the application of topical mydriatics (such as high concentration cyclopentolate 2% and phenylephrine 10%). Some studies favour the addition of preoperative epinephrine and topical nonsteroidal anti–inflammatory drugs (e.g. flurbiprofen, ketorolac), due to its advantage in the blockage of prostaglandins which cause miosis during surgery.[19,20]

Intraoperative preventive measures

Strategies for managing progressive miosis and iris stroma billowing during surgery in IFIS patients include:

- **Irrigation of epinephrine**: preservative-free solution of epinephrine 1:10.000 may increase pupil diameter when injected the anterior chamber at the start of surgery.[20]
- **Intracameral injection of epinephrine and phenylephrine:** promote maximal dilation, augment iris muscular tone and therefore reduce the propensity for billowing and subsequent prolapse in cases of IFIS. They may be used in the beginning or during the surgery, depending on pupil behaviour. Despite few reports of adverse reactions, attention is advised to potential toxicities: local toxicity to endothelium, systemic side effects such as spikes in blood pressure, cystoid macular oedema and toxic anterior segment syndrome.[21]
  - **Intracameral epinephrine**: avoid reserved solutions and use a diluted mixture to avoid corneal endothelial damage [e.g. dilution 1:3 with balanced salt solution (BSS), resulting in a 1:4.000 epinephrine solution].[4]
  - **Intracameral phenylephrine**: protocols for accurate preparation and dosing are inconsistent, so clinical use may be variable. Solutions should be preservative and bisulfite free. It has been proposed that 0.25 mL of phenylephrine 2.5% (Minims) should be increased to 2.0 mL using BSS prior to use; they also recommend that at least 30 seconds be allowed for maximal effect.[21]
- **Sub-Tenon injection of 2.5 ml of 2% lidocaine** was found to decrease the incidence of IFIS features in patients taking oral α-adrenergic inhibitors when compared to intracameral lidocaine.[22]

Surgical technique modifications

Multiple technique modifications may be employed during cataract surgery in IFIS and small pupil cases, which have been proposed to reduce overall complication rates:

- Creation of appropriately sized tunnels and entry anterior to the iris root, reducing wound leak.[4]
- Use of ophthalmic viscosurgical devices (OVDs): viscomydriasis using high concentration sodium hyaluronate (such as Healon5®) has been used in IFIS with high success. This cohesive OVR has the ability to dilate the small pupil effectively and also to create a physical barrier to decrease iris billowing and prolapse through the incisions. However, the latter effect depends on Healon5 to remain in the anterior chamber throughout the procedure, which requires measures like the use of low aspiration flow and vacuum settings.[8,21] If high vacuum settings are needed (e.g. dense nucleus), a dispersive OVR may be injected peripherally, followed by central injection of Healon5, so the former remains in the anterior chamber closer to the cornea and provides stability of intraoperative mydriasis – this technique is known as modified soft-shell technique.[4,19]
- Careful hydrodissection: it is important to ensure that the anterior chamber is not overfilled with OVDs in order to prevent iris prolapse during hydrodissection. In IFIS, hydrodissection and hydrodelineation are two of the surgical maneuvers which represent more risk of iris prolapse. Attempts should be made to ensure decreased irrigation and aspiration flow rates and direct irrigation currents above the iris plane and away from the pupillary margin to reduce the degree of anterior displacement of the lens–iris diaphragm, preventing the iris from prolapsing.[21] In the presence of iris prolapsing tendency, it has been suggested to bowl out a small portion of central endonucleus, followed by hydrodelineation from inside-out,

resulting in an ability to rotate the endonucleus and then chop the residual endonuclear bowl in the usual manner.[20]

- Bimanual microincision phacoemulsification: useful in soft to moderate nuclear densities due to the small sized incisions, making iris prolapse thought the incisions then less likely. Combination of this technique with the use of Healon5 is very advantageous in cases of dense nuclei, where the pupil may remain dilated and enable larger capsulorrhexis. The irrigator should be kept in an anterior position when removing the remaining cortical material with the phacoemulsification needle, in order to maintain a posterior placed iris and hindering its billowing and concomitant pupil constriction.
- IOL implantation: the cartridge of the injection system should be turned bevel-up while introducing it to avoid prolapse of iris into the cartridge, as well as after the lens is placed in the bag and exiting the eye.[20]
- Pupil enlargement devices: they provide dilation of the small pupil, prevent constriction of the pupil and restrain the iris from prolapsing. They are recommended in cases with predictive factors of severe IFIS (e.g. poor preoperative pupil dilation).[4]
    - **Pupil expansion rings** – generally easy to insert and remove from the eye, less traumatic than iris retractors as they do not overstretch the iris, require less surgery time and do not require additional incisions. Currently available designs include Morcher Pupil Ring®, Milvella Perfect Pupil®, Malyugin Ring®, Xpand^{NT} iris speculum, Visitec i-Ring Pupil Expander and B-HEX pupil expander®. The rings are introduced following incision completion and injection of dispersive viscoelastic. It is important to ensure correct position of the ring prior to removing it with the injector after IOL implantation, in order to prevent injury to intraocular ocular contents.[20]
    - **Iris retractors/hooks** – very commonly used in the management of IFIS, these devices maintain a constant pupil size during surgery, have lower costs than pupil rings and offer a better safety profile in shallow anterior chambers. There are different techniques for placing the hooks. Placing four hooks in a diamond configuration demonstrates advantages in IFIS as suggested by the American Society of Cataract and Refractive Surgery committee.[4] In addition to maximization of pupillary dilation in front of the phaco tip and thus facilitation of cataract space removal[8], this configuration includes a subincisional retractor inserted through a separate plane. Thus, it allows the iris to be pulled posteriorly and away from the phaco tip and incision, preventing iris prolapse and iatrogenic iris trauma. There are disposable (6-0 nylon manufactured material) and reusable retractors (4-0 polypropylene) available, the latter being the same size and rigidity as an IOL haptic and thus more easily manipulated.[4] Moreover, iris retractors are advantageous during the placement of a toric IOL, since two of the retractors being used can be aligned with the astigmatic axis.[17]
- Combination strategies: as there are no reliable methods to predict the severity of IFIS in advance, different modalities may have complementary advantages when combined, particularly because clinical circumstances may change during surgery.[4] In more challenging cases, such as a small pupil with concomitant tamsulosin use, pseudoexfoliation and shallow anterior chamber, it may be preferable to undergo 25-gauge pars plana vitrectomy as the first step of the surgery.[20] As reported sphincterotomies (including partial thickness) and mechanical stretching of the pupil are not effective and may exacerbate IFIS.[1]

Management

Management of small pupils

There are other clinical entities which may present with small pupils without the other features of IFIS, mainly pseudoexfoliation, diabetes mellitus and glaucoma. In these cases, there are several surgical techniques available which may facilitate pupil dilation and visualization during phacoemulsification.

In addition to the anteriorly described strategies, intraoperative efficient options to mechanically stretch the pupil are available for small pupils unrelated to IFIS. The latter techniques are not advantageous and may exacerbate IFIS.

Methods for *mechanical stretching of the pupil* include the following:

- When poor dilation is caused by posterior synechiae and there is normal zonular support, the synechiae should be lysed with a metallic spatula or cannula, followed by the injection of OVD to disrupt the irido-capsular adhesions if needed. Following dissection of the synechiae, additional dispersive OVR may be injected in the centre of the pupil to achieve greater pupillary dilation.
- Manipulation of phacoemulsification instruments: it is possible to retract the pupil and increase its size through the incisions, but it is highly dependent on experienced surgeons with the correct technique to avoid thermal injury and focal depigmentation.
- Bimanual pupil stretching technique of Luther Fry: it requires two hooks engaged at opposite pupillary ends to create a 5-6 mm pupilar diameter, with the adjunctive use of an OVR to protect the anterior lens capsule.
- Beehler pupil dilator: single instrument which provides a pupil diameter of 6–7 mm by making

microsphincterotomies circumferentially around the pupil and can be mechanically reduced at the end of the procedure. This technique preserves a functional pupil size and is particularly useful in cases where pupil margin is fibrotic (e.g. with chronic use of pilocarpine). However, some cases require a miotic agent after surgery to prevent the formation of synechiae.

- Iris sphincterotomy: examples include proximal superior small segment excision, midiris iridectomy followed by sphincterotomy and multiple partial thickness cuts in iris sphincter using intraocular microscissors prior to stretching.[17,20]

Complications

Complications during phacoemulsification surgery in IFIS patients vary in severity, including iatrogenic iris injury, wound dehiscence, hyphema, iridodialysis, nuclear drop, posterior capsule rupture and vitreous loss. Furthermore, the propensity of the iris to prolapse towards the phaco tip and to the incisions increases the risk of postoperative uveitis and permanent pupil distortion with glare and photophobia[4]. Other long-term consequences include retinal-detachment, cystoid macular oedema and limited visual recovery due to endophthalmitis.[23] Adequate preoperative evaluation and use of preventive measures anticipating IFIS significantly reduces the rates of complications.[1]

Conclusion

IFIS remains highly attributable to the drug-induced blockage of α1-1A receptor found in the iris dilator muscle, with a large proportion of patients under or with history of previous treatment with tamsulosin. It is important to recognize the rising frequency of women taking these drugs mainly for urinary retention and hypertension, constituting potential IFIS cases. Primary care physicians and urologists should likewise be aware of the association between tamsulosin and increased complication rate in cataract surgery. Discontinuing tamsulosin prior to surgery has no significant benefit and does not prevent IFIS.

Anticipation of IFIS before surgery should be part of ophthalmologists' preoperative assessment in order to achieve appropriate preparation for the procedure. Lack of preoperative prophylaxis is linked to higher rate of complications and worse visual outcomes. Moreover, further clinical trials and studies are needed to create a standardised assessment that stratifies the risk and predicts IFIS, as well as to compare the efficacy and safety profile of the different management options for IFIS.

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Surgical Techniques for Refractory Macular Holes

- Dr. Unnikrishnan Nair

Chaithanya Eye Hospital and Research Institute, Trivandrum, Kerala

Introduction

Until 1991, observation was the standard of care for macular holes (MHs). In 1991, Kelly and Wendel introduced pars plan vitrectomy (PPV) with peeling of any associated epiretinal membrane (ERM) and gas tamponade for primary repair of idiopathic MHs, with a 58% successful closure rate.[1] This seminal work stimulated the interest in refining the surgical techniques. In 1997, Eckart et al [2] proposed the technique of PPV, internal limiting membrane (ILM) peeling with perfluoropropane (C3F8) gas as a tamponade for surgical repair of MH. The results of this technique were impressive with a 92% closure rate. It was postulated that ILM peeling minimizes the epiretinal tangential traction and stimulates a strong glial tissue response, which helps with MH closure.[2,3] While advances in vitreoretinal surgical techniques resulted in high success rates of surgical repair of MH, recurrence or persistence of MH after surgery may still occur.[2] The term refractory MH describes a persistent MH that remains open after surgical repair. In contrast, a reopened MH refers to a MH that closed initially after surgical repair and then reopened.[4] It is important to differentiate between the 2 terms as they have different visual and anatomical prognosis after repeat surgery, with the success rate in reopened MHs being higher.[5]

Yoshida and Kishi,[6] found that reopening of MH after surgical repair was mainly caused by recurring ERM. With ILM peeling, reopening has become less frequent, indicating the role of ILM removal in preventing reopening of MHs.[3] Histopathologic studies examining the residual ILM in the second surgery for refractory MH have shown significant proliferation of cells with new collagen formation at edge of the remaining ILM.[7] Residual ILM remnants and collagen following PPV with ILM removal may act as a stimulus for formation of glial tissues which then exert tangential traction on the edges of the MH preventing its closure or resulting in reopening after closure.[7,8] While thinning of ganglion cell layer and dissociated optic nerve layer have been reported after ILM removal, no functional consequences have been associated with these anatomical changes.[9]

Incidence of Refractory MH

D'Souza et al [10] reported an incidence of refractory MH of 9% in their study that included 491 patients with MH who underwent PPV and ILM removal. This was higher than the 4.2% rate of persistent MH reported by Jackson et al [11] who studied 1078 eyes after PPV combined with ILM removal for MH repair. Surgical failure of primary MH repair may be the result of risk factors related to the clinical features of MH or to the operative variations and postoperative positioning.

Clinical Features Associated With Increased Risk of Failure of Surgical Repair of MH

MH Size and Stage

Stage 4 MH has lower closure rates and worse visual acuity outcomes after surgical repair in comparison with stage 2 and 3 as reported by Williamson et al.[12] Moreover, a larger MH size is a well-known independent risk factor for lower success rates after MH surgery as demonstrated by the Manchester large MH study.[13] This study showed ~90% successful closure rate after PPV and ILM removal for MH size between 400 and 649µ The success rate of MH closure decreased to 76% for holes 650 to 1416µ highlighting the importance of the MH size as a prognostic factor for surgical repair.[14]

MH Chronicity

While repair of long-standing MH can still achieve improvement of vision,[15-17] there is a higher closure rate for MH repaired within 1 year of the onset of symptoms, with about 50% decline in the rate of successful repair after 1 year.[15] Early surgical repair of MH is recommended to achieve the best anatomical and visual outcomes.[18]

High Myopia

High myopia (myopia of -6 Diopters or more) is a well-recognized risk factor for failure of MH repair with poorer visual outcomes.[19] Multiple studies suggested that the long axial length (AL) and posterior staphyloma induce traction over the edges of the MH, which impairs its anatomical closure.[20-22] Suda et al [22] reported that AL >30 mm is associated with increased risk of failure of

the initial surgical repair of MH. Tsung-Tien Wu and Ya-Hsin Kung showed that anatomical closure of MH was seen in 62.5% of eyes with high myopia, compared with 94.1% in eyes without high myopia. Even with successful MH closure in highly myopic eyes, the visual acuity gain is usually limited when compared with the eyes without high myopia.[19,23,24] With development of MH, fluid may access the subretinal space from the MH, resulting in myopic macular hole retinal detachment (MHRD), which is more challenging to repair.[25,26] Retinoschisis at the fovea (foveoschisis) is an additional risk factor in highly myopic MH cases with worse anatomical and visual outcomes.[20,21,27]

Management of Refractory MH

Surgical approaches include MH scaffolds, use of adjuvant agents to promote tissue growth, and tissue replacement using autologous retinal transplant (ARTs) and subretinal fluid application. In the following section, we will evaluate the main strategies and the variable modifications.

(1) MH scaffolds

(A) ILM as a scaffold in refractory MH

It was found that the peeled ILM in MH cases contains Muller cells.[28] Moreover, histopathologic studies have confirmed the role of Muller cells in promoting gliosis.[28-31] Therefore, it was postulated that using ILM as a scaffold in MH cases might promote tissue regeneration and closure of MH.[32]

Inverted ILM flap

In 2010, Michalewska et al[32] introduced the inverted ILM flap technique. In this technique, instead of the standard complete ILM separation from the MH, the ILM is peeled toward the center of the MH without complete separation from the edges of the MH. The ILM is kept attached to the edges of the MH while being inverted upside down to cover the MH followed by fluid-air exchange. The study showed a closure rate of 98% with inverted ILM flap in stage 4 MH with size more than 400 [micro]m (flat-open configuration in 2%) compared with 88% closure rate with complete ILM peel (flat-open configuration in 19%). The authors attributed the superior outcomes of this technique to the gliosis-inducing effect of the ILM along with providing structural support to the growing tissues facilitating successful closure. Visual acuity outcomes have been correlated to the higher rates of external limiting membrane and ellipsoid zone recovery in eyes that underwent inverted ILM flaps.[33,34] The inverted ILM flap has shown superior anatomical and visual outcomes especially with larger MH in several reports.[32,35-41] Shen et al [38] performed a meta-analysis of studies that evaluated the ILM flap versus a complete ILM peel for MH >400 [mu]m. The review included 4 retrospective studies and 4 randomized controlled trials. The analysis showed significantly higher rate of MH closure among inverted ILM flap groups with superior visual acuity gain in the first 3 months after surgical repair, but there was no difference at the 6-month follow-up visit.

Compared with the standard ILM peeling, the inverted ILM flap in MHRD has demonstrated higher success rates of closure, retinal reattachment, and similar or superior visual acuity outcomes.[33,34,42-46]

An important intraoperative limitation of the inverted ILM technique is the possible amputation of the inverted ILM flap during the fluid-air exchange. Using the perfluoro-n-octane (PFO) or viscoelastic can stabilize the flap and prevent amputation of the inverted ILM flap until completing the fluid-air exchange.[47,48] A slow fluid-air exchange also helps with this.

Michalewska and Nawrocki,[49] have also demonstrated that surgical failure in these cases is because of the retraction of the ILM flap to its original position leaving the MH uncovered. Repeat surgery may include repositing the flap into the MH with the use of either air or silicone oil to stabilize the flap. Results showed no difference in the anatomical or visual outcomes with air compared with silicone oil. Success rate of MH closure was 89% after the second surgery and 100% after the third surgery.[49]

Modifications of the inverted ILM flap technique

Several studies have proposed various configuration of the ILM flap hinge placement, flap size and flap positioning over the MH.[50-53] These variations showed overall similar functional and anatomic outcomes and more flexibility for the surgeons to choose their preferred technique, which should be tailored to each case.[50,53-55] Chou et al [56] showed that either temporal or nasal ILM flap may similarly improve MH closure rates as long as the ILM flap is properly positioned and secured over the MH.

The inverted temporal flap technique

The ILM is peeled only temporal to the fovea while kept attached to the temporal edge of the MH followed by its inversion nasally to cover the MH.[54] This technique preserves the ILM nasal to the fovea with the purpose of mitigating any potential iatrogenic complications to the papillomacular bundle.[54] Takai et al [57] have demonstrated more stability to the ILM flap with this technique.[32,57] One limitation of this technique is potential postoperative contraction, especially in younger patients, as reported recently by Hirata et al.[58]

Autologous free ILM flap

Morizane et al [59] introduced the technique of autologous ILM free flap in cases with prior ILM peel. In this technique, residual ILM and area of previous ILM peel are identified using a stain. A small piece of ILM with the same size of the MH is then peeled to create an autologous free ILM flap. This is followed by turning off the infusion line and placing the free flap inside the MH. To avoid amputation of the flap during fluid-air exchange,

viscoelastic material is placed over the free ILM flap. This is followed by reopening the infusion line and a slow fluid-air exchange.[59,60] Rossi et al [61] compared the outcomes of performing a free autologous ILM flap versus a control group who underwent widening of the area of ILM peel on repeat surgery for refractory MH and reported a success rate of 93.3% with ILM free flap versus 64.2% success rate of closure of controls, with greater gain in visual acuity at 3 months.

Intraoperative stabilization of the autologous free ILM flap over the MH is challenging. Flap displacement or accidental extrusion during fluid-air exchange might occur.[18] Viscoelastic-assisted or PFC-assisted free ILM flap technique has been utilized to improve the stabilization and secure the flap over the MH.[59,62] Harvesting a free ILM flap and tucking it inside the MH has also been proposed to minimize the risk of flap displacement.[63] However, this technique might increase the risk of potential damage to the underlying RPE and photoreceptors.[63] To overcome the potential risk of intraoperative loss or displacement of the ILM flap, the ILM pedicle flap transposition and the superior wide-based ILM flap transposition (SWIFT) techniques were introduced.

ILM pedicle flap

A strip of the residual ILM is peeled in a circumferential manner starting inferior to the macula and extending superiorly leaving a pedunculated ILM flap. The pedunculated ILM flap is then inverted and positioned over the MH followed by air tamponade.[51,64] However, this technique has not been widely adopted as the ILM strip and the flap hinge are small and prone to displacement and retraction with reopening of the MH.[18,65]

Superior Wide-Base ILM flap Transposition (SWIFT) technique

A wide-based ILM flap is fashioned from the ILM over the superior macula. The flap is then inverted to cover the MH. Tabandeh et al [65] showed closure of MH in 94% of all cases with 100% closure rate in refractory MH cases with prior ILM peel.

The ILM retracting door for myopic MH

In 2019, Finn and Mahmoud [66] developed the ILM retracting door technique for myopic MH. In this technique, the ILM is peeled on the nasal side of the MH while leaving a hinge temporal to the MH. After releasing the tangential traction induced by the taut ILM in highly myopic eyes, it was proposed that the myopic contour of the globe can facilitate temporal retraction of the ILM flap to cover the MH. One advantage of the technique is preserving more ILM to use for potential future surgeries in these complicated myopic MH cases.[18,66,67]

(B) Alternative scaffold tissues

Amniotic Membrane Graft (AMG)

The human amniotic membrane graft (AMG) can be used as scaffold in refractory MH cases. It can facilitate MH closure through acting as a scaffold supporting tissue growth as well as its potential ability to release growth factors that can help with tissue regeneration.[67-72]

In 2019, Rizzo et al [69] introduced the technique of AMG implantation into the subretinal space in refractory and myopic MHs. In this technique, chandelier light was used to allow bimanual manipulation of the AMG which was inserted under the MH in the subretinal space using PFO for AMG stabilization. Intraoperative optical coherence tomography (OCT) was used to confirm the proper positioning of the AMG and SF6 gas was used as a tamponade. Postoperative OCT showed the AMG plugging the MH, closing it at week 1 visit after the surgery. No adverse events were reported over 1 year of follow up, and visual acuity continued to improve up to 6 months postoperatively. In consecutive studies by Caporossi and colleagues, the authors studied different aspects and uses of applying AMG in refractory MHs.[68,70,71,73] In a study that included 36 eyes with persistent MH after prior PPV and ILM peel, Caporossi et al [70] utilized the AMG to plug the MH, which resulted in a successful closure rate of 100%. There was improvement in mean 6-month visual acuity from 1.15 (Snellen equivalent 20/300) +/-0.14 logarithm of the minimum angle of resolution (logMAR) to 0.65 (Snellen equivalent 20/80) +/-0.26 logMAR. Adaptive optics images showed the presence of photoreceptors while microperimetry detected partial macular sensitivity at the edges of the AMG. Anatomically, postoperative OCT showed tissue regeneration above the AMG with a segmentation pattern similar to the retinal layers. These anatomical and functional results were further validated in a comparative study by Pacini et al.[73] The study showed higher cone density on adaptive optics with reformation of the normal foveal depression on OCT in cases of refractory MHs treated with AMG compared with cases treated with autologous ILM transplant, which showed less cone density and subverted foveal contour.[73] In another study by Caporossi et al,[68] the authors reported a successful closure rate of 94% in cases of recurrent myopic MH with AL >30 mm. Caporossi et al [71] also demonstrated that air was similar to SF6 as an endotamponade after AMG implantation.

Lens capsular flap

In 2016, Chen and Yang [74] introduced the lens capsule as a scaffold in refractory MH and MHRD cases. The lens capsular flap was harvested from either the anterior or posterior lens capsule depending on the lens status of the patient. The flap was then placed within the hole and secured in position by placing the edges of the flap under the edges of the MH. This technique showed positive results in these challenging cases with a 75% successful closure rate.[74] More recently, Peng et al [75] reported a higher success rate of this technique with 96% closure rate in 50 eyes with refractory MHs. The authors used either

autologous or allogenic lens capsular flap, trimmed to estimate the size of the MH as a scaffold tissue to seal the MH with no reported major complications. The median visual acuity improved from 1.78 logMAR (median Snellen acuity: 20/1200) to 1.00 logMAR (median Snellen acuity: 20/200).

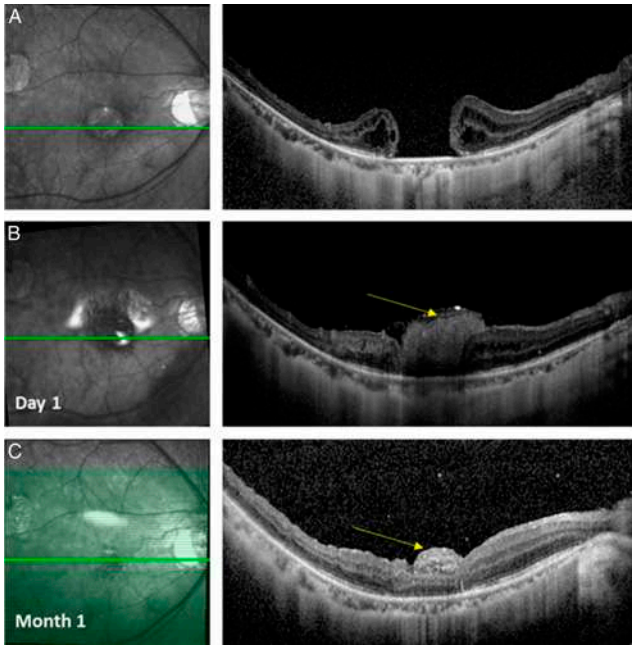
(2) Autologous platelet-rich plasma (PRP) and adjuvants

In the 1990s, the intraoperative use of therapeutics that can promote healing and tissue proliferation was first introduced as an adjunct agent during surgical repair of MH. This included use of growth factors in autologous serum, transforming growth factor B2, and autologous platelet concentrates.[76-78] More recently, the use of these growth factors has regained popularity in treating refractory MHs including large and myopic MHs.[79] In this technique, 10 mL of venous blood is collected first from the patient just before the surgery and stored in a sterile 10 mL tube containing 1 mL of 3.2% sodium citrate to prevent coagulation. The tube is then centrifuged at a rate of 1600 revolutions per minute (rpm) for 10 minutes. This results in separation of the patient›s blood into 3 visible layers from top to bottom: platelet-poor plasma, platelet-rich plasma (PRP) and red blood cells. PRP is then collected in a sterile 3 mL syringe.[80-82] Figueroa et al [82] used autologous PRP in 7 eyes with highly myopic MHs. All eyes achieved successful closure with mean improvement of one line in vision. Purtskhvanidze et al [83] demonstrated an 85% closure rate in refractory MH cases with prior PPV and ILM peel. However, 1 patient developed postoperative rhegmatogenous retinal detachment without macular involvement which was successfully repaired with PPV and C2F8 gas endotamponade

(3) Tissue replacement using ART

In 2016, Grewal and Mahmoud [84] introduced the technique of ART which was initially described in a case with high myopic refractory MH with multiple prior surgeries. The technique included harvesting an autologous neurosensory retinal flap outside the arcade, often superonasal to the superior arcade to facilitate effective tamponade but harvest locations may vary depending on the retinal anatomy. Endolaser barricade is applied to the planned donor site followed by endodiathermy to the blood vessels at the site edge. Chandelier light can be used to allow for bimanual manipulation of the graft, which was cut by vertical scissors and transposed to cover the refractory 1100 [mu]m MH under PFO. This is followed by direct PFC-silicone exchange. The results of this technique were impressive with visual acuity recovery to 20/80 in the initial report. The restoration of the outer retinal layers and corresponding functional improvement may be partially explained by the concept of ectopic synaptogenesis. Ectopic synaptogenesis has been demonstrated in animal models, wherein rod photoreceptors have been shown to form functional ectopic synapse with cone bipolar cells.[85] On the basis of this observation, it was hypothesized that the transplanted rod photoreceptors from peripheral ART grafts might behave similarly and form ectopic synapses with cone bipolar cells which would partially explain the restoration of the function and anatomy of the outer retinal layers.

In a multicenter study by Grewal and colleagues, the authors described the ART technique in 41 eyes with refractory MH with prior PPV and complete ILM peel. Results showed successful MH closure on OCT in 88% of eyes (Fig. 1).[86] Mean corrected visual acuity measured by logMAR improved from 1.11+/-0.66 to 1.03+/-0.51 (*P*=0.03) at the last postoperative visit. Major postoperative complications were vitreous hemorrhage in 1 case and retinal detachment in 1 case. Retinal flap dislocation was also seen in 2 cases. Short-term PFCL tamponade has also been described as an option with this procedure wherein the patient is positioned supine and the PFCL is removed after 2 weeks



In a study by Tanaka et al,[87] the authors used ART technique for primary repair of large MHs with MH diameter between 643 and 1214 [micro]m. The results showed successful MH closure in all cases with significant improvement in mean visual acuity.[87]

More recently, the global ART study group have published the results of ART in 130 eyes with primary MH (n=35), refractory MH (n=76), and MHRD (n=19).[88] Mean maximum MH diameter was 1470+/-160 [mu]m and mean minimum diameter was 840+/-94 [mu]m. Closure rate in these large refractory holes was 89% in MHs cases with 95% closure rate in MHRD. There were at least 3 lines of visual acuity improvement in 43% of eyes and at least 5 lines of visual acuity improvement in 29% of eyes. Complications overall were rare and included ART graft dislocation in 5 cases, 5 cases of postoperative retinal detachment and

1 case of endophthalmitis. A small dislocation of the ART graft can be corrected by gently manipulating the graft during silicone oil or perfluorocarbon removal surgery, however, if the ART is completely dislocated form the MH, a repeat graft may be required and can be successfully performed.

(4) Subretinal fluid application

Some studies have attributed the failure of closure of large chronic MH even after eliminating all the tangential traction forces to be because of the subretinal adhesions between the RPE and neurosensory retina at the edges of MHs.[89-91] Subretinal fluid application with induction of small macular detachment have been proposed to release these adhesions.[89-91] In this technique, 2 to 3 small subretinal blebs are created using 41-guage subretinal cannula under a 2-disc diameter PFO bubble over the MH. This is followed by drainage of PFO and injecting more subretinal fluid to cause the small subretinal blebs to become confluent into one small macular detachment. The small macular detachment releases the adhesions between the retina and RPE and allows more mobility of the retina at the edges of the MH. In the APOSTEL study,[91] the authors applied this technique in 41 eyes with persistent MH after prior PPV, ERM, and ILM removal. Results showed successful closure of refractory MH in 85% of cases with improvement of mean visual acuity from 0.1 (Snellen equivalent 20/200) to 0.22 (Snellen equivalent 20/100). No major adverse events were reported although there have been reports of retinal pigment epithelium atrophy in the area of subretinal bleb application as seen on fundus autofluorescence imaging.

Conclusion

Over the last decade, advances in surgical techniques have markedly improved the anatomical and functional outcomes in the challenging cases of refractory, large chronic, high myopic MH and MHRD. In this review, we have discussed the commonly adopted techniques in tackling these challenging cases. Table 1 summarizes the recommendations for the management of refractory MHs based on our literature review. While there is currently no consensus on the procedure of choice in these cases, the inverted ILM flap techniques are best considered for eyes with some residual ILM that is relatively close to the MH to enable flap inversion. The free ILM flap may be considered in eyes with residual ILM that is too distant from MH. The AMG, ART and subretinal fluid techniques should be considered in eyes with large MH (>650 [mu]m)

or with refractory MH when the use of an ILM flap is not feasible.[18,67] Subretinal fluid application could also be considered for smaller refractory MHs with no available ILM.

Table 1-Recommended techniques for refractory macular hole

Refractory macular hole characterstics	Recommended technique
Prior PPV with ILM peel with residual ILM close to MH	Inverted ILM flap technique
Prior PPV with ILM peel with residual ILM distant from MH	Consider free ILM flap, AMG, ART, Subretinal fluid application
Prior PPV and ILM peel no available ILM	Consider AMG, ART or subretinal fluid application

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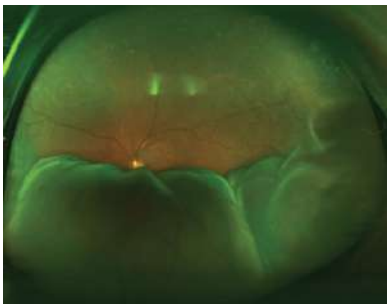
Partial thickness sclerectomy (PTS) for the management of Uveal Effusion

- Dr. Isabella V. Wagner[1], Dr. Adrian Zarraga Pereda[1], Dr. Christian Draper[1], Dr. Syril Dorairaj[1]

[1]Department of Ophthalmology, Mayo Clinic, Jacksonville, Florida, USA

Uveal effusion was first described by Schepens and Brockhurst[1] in 1963 and an association between nanophthalmos and/or abnormal sclera was first described by Brockhurst in 1975.[2] Idiopathic uveal effusion or uveal effusion syndrome (UES) is characterized by spontaneous ciliochoroidal detachment, and the diagnosis is made when these findings occur in the absence of hypotony, inflammation, or other etiologies associated with choroidal detachment.[3] Early clinical findings in UES include serous detachment of the choroid beginning in the periphery with secondary retinal detachment, loss of visual field, and a shallow anterior chamber with normal intraocular pressure. Retinal pigment epithelial changes, described as "leopard spots," are characteristic late clinical features of this disease.[4] Visual impairment most commonly results from serous retinal detachment involving the macula. Typically, middle-aged, healthy males are affected, and the disease generally presents unilaterally. Schepens1 and Brockhurst2 suggested that the subretinal and suprachoroidal fluid accumulation in eyes with uveal effusion resulted from congestion of the choroidal venous system secondary to compression of the vortex veins by thick sclera. Gass[5] hypothesized that the underlying cause of UES is a congenital anomaly of the sclera and possibly of the vortex veins, which leads to impaired transscleral outflow of intraocular protein, causing a serous detachment of the choroid, ciliary body, and retina. Histopathologic studies have demonstrated scleral abnormalities in patients with nanophthalmos.[6] These include scleral thickening and derangement in the organization of the collagen fibrils with larger bundles oriented at an angle with respect to the surface of the globe, compared with the normal parallel orientation.[6]



Since scleral thickening and abnormality has been thought to contribute to the development of uveal effusion in nanophthalmos and UES, various surgical techniques targeting the sclera have been developed. These techniques include decompression of the sclera around the vortex veins,[7] PTS in some or all quadrants without decompression near the vortex veins,[8] and full-thickness sclerectomy under a partial-thickness scleral flap.3 Late fibrosis and scarring can occur after surgical intervention, and some patients require multiple procedures. As there is a greater risk of choroidal perforation and retinal incarceration during these repeat procedures, the use of a scleral punch to facilitate dissection in the intended surgical plane with adjuvant mitomycin C (MMC) to inhibit further scarring has been suggested for revision surgeries.[9,10] As our understanding of UES expands, novel surgical interventions, aiming to minimize risk and increase efficacy, have been described. One such technique entails creating a sclerotomy with a guarded diathermy probe (with a 2 mm penetrating tip) and facilitating choroidal fluid drainage with an anterior chamber infusion.[11] Another technique, described by Kong et al,[12] requires creating a drainage sclerotomy, without vortex vein decompression or sclerectomy and with a full-thickness square bracket–shaped scleral incision and sutured edges. Yepez et al[13] reported using a glaucoma drainage device (Ex-PRESS shunt; Alcon Laboratories, Fort Worth, TX), inserted using a sclerotomy, to facilitate the continuous drainage of suprachoroidal fluid. These surgical procedures and techniques have varying degrees of success, and some patients require multiple procedures. In this report, we describe our graded surgical approach and outcomes in a series of six eyes of four patients with nanophthalmos and/or idiopathic UES.

Surgical Technique

"Sclerectomy" refers to partial-thickness excision of a portion of the sclera, and "sclerostomy" refers to the creation of a small, full-thickness opening through the sclera using a blade or punch. Informed consent was obtained from all patients. All procedures were performed under general anesthesia, and standard asepsis and antisepsis techniques, using 5% povidone-iodine, were employed. At the end of the surgical procedure, patients received subconjunctival injection of antibiotic and corticosteroid.

Partial-Thickness Sclerectomy

After a 360° conjunctival peritomy was performed, the rectus muscles were isolated and bare sclera was exposed in all four quadrants. The vortex veins were identified, and two-thirds thickness sclerectomies were performed in using a #64 or #57 blade. The sclerectomies measured approximately 4 mm · 4 mm and started 1 mm posterior to the muscle insertion. Care was taken to avoid the vortex veins. No choroidal or subretinal fluid drainage was performed.

Partial-Thickness Sclerectomy With Mitomycin C

A 360° conjunctival peritomy was performed, and PTSs were created as described above. After this, a sponge soaked in MMC 0.4 mg/mL was placed on the sclerectomy for 2 minutes in each quadrant. Immediately after removal of the sponge, the sclera was thoroughly rinsed with balanced salt solution, and after MMC application in the last quadrant, the entire ocular surface was rinsed again. No choroidal or subretinal fluid drainage was performed.

Partial-Thickness Sclerectomy with Punch Sclerostomy and Subretinal Fluid Drainage

After a 360° conjunctival peritomy was performed, PTSs were created as described above and enlarged in each quadrant using a #64 or #57 blade. Additional thinning of the windows was performed with lamellar dissection until the blue/brown appearance of the choroid was visualized. In the center of the window in the inferonasal quadrant, a scleral cutdown was performed until bare choroid was exposed. A Kelly punch was then used to make a full-thickness sclerostomy, allowing for egress of suprachoroidal fluid. Argon green laser (600 mW and 0.5 seconds duration) was applied to the choroid in the area of planned drainage with a 20-gauge (G) endolaser probe. Laser treatment was applied until the choroid blanched. A 30 G needle was used to penetrate the choroid through the area of laser, allowing for drainage of subretinal fluid. Intraocular pressure was maintained with intermittent intraocular injections of balanced salt solution. Full-thickness sclerostomies were created in a similar fashion in two of the remaining three quadrants.

Partial-Thickness Sclerectomy with Vortex Vein Decompression

A 360° conjunctival peritomy was performed and PTSs were enlarged using a #64 or #57 blade. During this dissection, the vortex vein was meticulously unroofed in each quadrant using the technique described by Brockhurst.[7] No choroidal or subretinal fluid drainage was performed. We reviewed the surgical techniques and clinical outcomes of six eyes of four patients with the diagnosis of nanophthalmos, idiopathic UES, or nanophthalmic uveal effusion. Axial length was, 24 mm in five eyes and, 20 mm in three eyes. All patients were men with a mean age of 63.75 years (range 52– 75 years) (Table 1). The mean number of surgeries per eye was 2 (range 1 to 4). The last performed surgical techniques included PTS in three eyes, PTS with MMC in one eye, PTS with punch sclerostomy and fluid drainage in one eye, and PTS with vortex vein decompression in one eye (Table 1).

Table 1. Characteristics of Patients Undergoing Scleral Surgery for the Management or Prevention of Uveal Effusion

Case#	Age, Years	Gender	Diagnosis	Laterality	No. Surgeries	Last Successful Surgical Technique
1	75	M	Nanophthalmos	Right	1	PTS
				Left	1	PTS
2	52	M	Nanophthalmos	Right	4	PTS + punch sclerostomy + fluid drainage
3	63	M	Nanophthalmos spectrum	Right	2	PTS + vortex vein decompression
				Left	2	PTS
4	65	M	Idiopathic UES	Right	2	PTS + MMC

M, male; UES, Uveal effusion syndrome.

Case 1 -A 75-year-old healthy man with cataracts was referred for evaluation and consideration for scleral surgery to prevent uveal effusion associated with cataract extraction. His family history was significant for nanophthalmos in two siblings. On examination, best-corrected visual acuity (BCVA) was 20/80 in the right eye and 20/60 in the left eye. The spherical equivalents were +20.00 diopters (D), and +18.50 D and axial lengths were 15.19 millimeters (mm) and 15.00 mm, in the right and the left eyes, respectively. Intraocular pressure was 15 mmHg in the right eye and 17 mmHg in the left eye. On slit lamp examination, no signs of inflammation were found in the anterior and posterior segments, and dense cataracts were confirmed in both eyes. B-scan ultrasonography revealed thick sclera without effusion or retinal detachment (Figure 1). We performed PTS, 12 weeks apart, in three quadrants, including inferonasal, inferotemporal, and superotemporal in the right eye and inferonasal, superonasal, and superotemporal in the left eye. He underwent cataract surgery in both eyes 1 month later. No uveal effusion developed during 3 years of follow-up

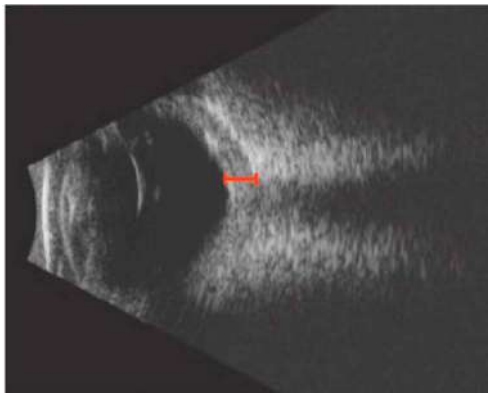


Figure. 1. B-scan ultrasonographic image in Case 1. B-scan ultrasonography of the right eye demonstrating abnormally thick sclera.

Case 2- A 52-year-old man with nanophthalmos and blurry vision, secondary to a Soemmering ring, in the right eye was referred for evaluation for scleral surgery to prevent uveal effusion before surgical removal of residual lens material. His ocular history was significant for uveal effusion and retinal detachment in the left eye for which he had a pars plana vitrectomy with silicone oil. At presentation, BCVA was 20/40 in the right eye and 20/800 in the left eye, and spherical equivalents were +21.00 D in both eyes. Intraocular pressure was 23 mmHg in the right eye and 16 mmHg in the left eye. B-scan ultrasonography of the right eye showed thick sclera and a mild choroidal effusion, with a choroidal thickness of 2.7 mm at posterior pole. Axial length was 16.50 mm in the right eye and unobtainable in the left eye because of the presence of silicone oil. We performed PTSs in all four quadrants in the right eye. At follow-up 1 year later, he developed uveal effusion with a serous retinal detachment (Figure 2, A and B). The Patient underwent various treatment approaches, including oral corticosteroids, topical dorzolamide, and immunosuppressive therapy with steroid-sparing agents for several months elsewhere, and no significant improvement was seen. Eventually, we repeated PTSs in all four quadrants by modification of the initial PTSs that had developed overlying fibrous tissue. There was complete resolution of uveal effusion and subretinal fluid postoperatively. At follow-up 5 months later, he had developed new subretinal fluid and a choroidal detachment, extending to the fovea. We performed a third procedure, this time supplementing PTSs in four quadrants with MMC. There was no improvement in the choroidal or retinal detachment postoperatively and vision was 20/300. After 3 months of observation, he underwent PTSs with punch sclerostomy in three quadrants (inferotemporal, superotemporal, and inferonasal), and subretinal fluid drainage. One week postoperatively, visual acuity had improved to 20/150, and choroidal and retinal detachments had improved dramatically. The retina was attached with leopard pattern pigmentary changes. At 3 months follow-up, BCVA was 20/100, and the subretinal fluid and choroidal detachment had resolved. At most recent evaluation, 18 months after his last surgery, BCVA was 20/70, and there was no recurrence of choroidal or retinal detachment (Figure 2, C and D).

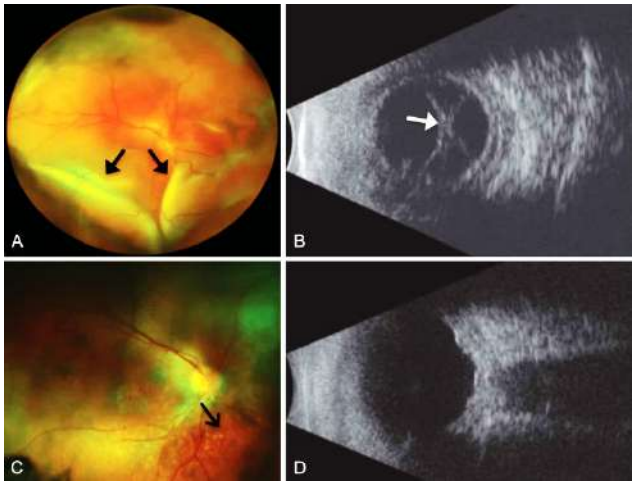


Figure. 2. Fundus photographs and B-scan ultrasonographic images of the right eye in Case 2. A. Fundus photograph and (B) B-scan ultrasonography demonstrating serous retinal detachment (arrows) inferiorly 1 year after the first PTS surgery. Attached retina and choroid with leopard pattern pigmentary changes (black arrow, open) can be seen in (C) fundus photograph, and (D) B-scan ultrasonography demonstrates resolution of retinal detachments.

Case 3- A 63-year-old man was referred for UES in the right eye (Figure 3A). At initial evaluation, his BCVA was 20/80 in the right eye and 20/30 in the left eye. Spherical equivalents were +3.75 D in the right eye and +1.75 D in the left eye. There was no inflammation in the anterior chamber in either eye, but there was trace cell in the anterior vitreous of the right eye. On dilated fundus examination, there was a speckled appearance to the retina and choroidal thickening with a shifting, exudative retinal detachment in the right eye. These findings were confirmed on B-scan ultrasonography. Axial length was 21.02 mm in the right eye and 21.76 mm in the left eye. He was started on oral Prednisone 40 mg to rule out any inflammatory cause, but no improvement was observed. We performed PTS in all four quadrants in the right eye. As there was no clinical improvement, a second procedure with vortex vein decompression in three quadrants (inferotemporal, inferonasal, and superotemporal) was performed. Shortly after, we performed prophylactic PTSs in three quadrants (superotemporal, superonasal, and inferotemporal) in the left eye before cataract surgery. Nine months after cataract surgery in the left eye, he developed UES with an inferior retinal detachment. We revised the PTSs in three quadrants and performed a PTS in the fourth quadrant in the left eye. At the most recentfollow-up visit, 5 years after the last surgery in the right eye and 4 years after the last surgery of the left eye, VA was 20/40 in the right eye and 20/25 in the left eye. The choroid and retina were attached. There were diffuse retinal pigment epithelial changes consistent with the typical leopard pattern associated with UES (Figure 3B).

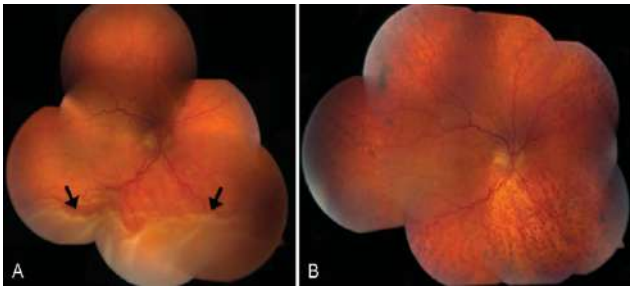
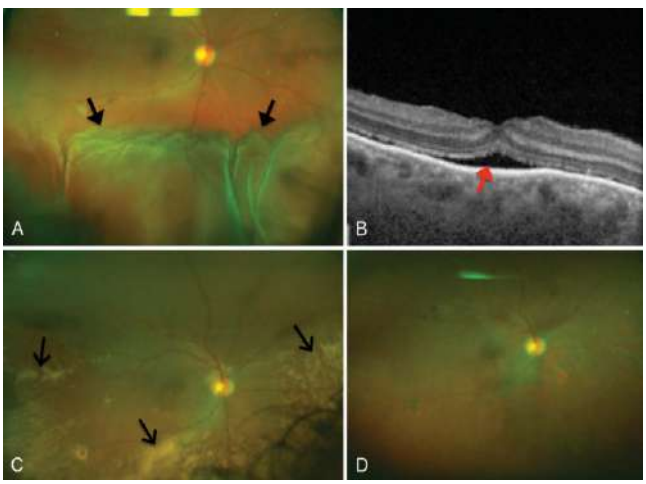


Figure. 3. Fundus photograph of the right eye in Case 3. A. Preoperatively there was a large peripheral choroidal effusion associated with a serous retinal detachment (black arrows), and (B) after the second surgery with partial-thickness sclerectomies and vortex vein decompression, the choroid and retina were attached with diffuse leopard pattern pigmentary changes.

Case 4 A 65-year-old man was referred for a serous retinal detachment in the inferior quadrant in the right eye after a choroidal biopsy excluded the presence of chronic inflammatory or malignant processes (Figure 4A). His BCVA was 20/70 in the right eye and 20/20 in the left eye with spherical equivalents of +0.50 D in the right eye and +1.50 D in the left eye. Intraocular pressure was 13 mmHg in the right eye and 14 mmHg in the left eye. No signs of inflammation were found on examination. Dilated fundus examination revealed subtle diffuse choroidal thickening with exudative detachment inferiorly extending beyond vascular arcade in the right eye and background diabetic retinopathy in both eyes. B-scan ultrasonography showed diffuse choroidal thickening in the right eye with a retinal detachment inferiorly and optical coherence tomography confirmed macular involvement. Axial length was 24.70 mm in the right eye and 24.02 mm in the left eye. As the serous detachment extended to macula, with decreased vision, the decision was made to perform scleral surgery (Figure 4B). We performed PTSs in three quadrants, including superonasal, inferonasal, and inferotemporal, in the right eye. A PTS was not performed superotemporally as the choroidal biopsy was previously performed in this area. Three months postoperatively, the choroid and retina were attached with extensive yellow subretinal precipitates inferiorly (Figure 4C). Five months later, there was a recurrent serous retinal detachment inferiorly in the right eye. As there was no improvement after 2 months of observation, PTSs with MMC was performed in all four quadrants. At follow-up 5 months later, the retinal detachment had resolved. The retina remained attached at follow-up 18 months after the second surgery, and the patient had a BCVA of 20/80 (Figure 4D).

Figure. 4. Fundus photograph and optical coherence tomography of the right eye in Case 4. A. Fundus photograph demonstrating bullous retinal detachment (black arrows) and (B) Optical coherence tomography showing macular involvement with subretinal fluid (red arrow). (C) The choroid and retina were attached with yellow subretinal precipitates (black arrows, open) 3 months after the first surgery with (D) improvement of the subretinal precipitates 1 year after the second surgery.



Discussion

Uveal effusion syndrome is a rare disorder, characterized by choroidal thickening, choroidal detachment, and serous retinal detachment that can be difficult to manage and often has a relapsing course. In our series of six eyes (4 patients) with nanophthalmos or UES, there was complete resolution or successful prevention of choroidal and retinal detachments in all eyes. In Case 1, prophylactic PTSs alone were effective. However, in Case 2, the choroidal and serous retinal detachments did not resolve until after the fourth surgery, which included PTSs with punch sclerostomies and subretinal and suprachoroidal fluid drainage. In Case 3, the choroidal and serous retinal detachments resolved in both eyes after the second surgery. There was resolution in the right eye after vortex vein decompression and in the left eye after 2 PTSs in all four quadrants. Two of these patients had nanophthalmos, and one had short axial lengths. In the fourth patient, no risk factors for UES were identified, and the sclera was visibly normal. Similar to Cases 2 and 3, in Case 4, there was complete resolution of the exudative retinal detachment after only two surgeries, the second of which was performed with MMC. In a study by Uyama et al [3] that aimed to evaluate surgical outcomes of subscleral sclerectomy for UES, three eyes required additional intervention. They performed the same subscleral sclerectomy procedure as a second surgery in two eyes andfull-thickness sclerectomy with removal of the scleral flap in one eye.[3] Kong et al[12] reported the surgical outcome of full-thickness sclerotomy in 5 cases of UES. In four eyes, exudative retinal detachment associated with UES resolved. One eye required three surgeries for resolution.[12] Similarly, Akduman et al,[10] described one patient that required PTS with MMC twice for resolution.10 In our series, the mean number of surgeries was 2. In Case 1, only one procedure was required to successfully prevent UES after cataract extraction, although in Case 2, four procedures were required.

UES is a diagnosis of exclusion and is often made after other causes of choroidal effusion have been eliminated. These include hypotony, inflammation and malignancy, and any associated or causative etiologies, such as trauma and medications.[4,14] Nanophthalmos is a developmental ocular disorder that results in a small eye with a short axial length, extreme hyperopia, shallow anterior chamber, high lens/globe ratio, and increased scleral thickness. Criteria for the diagnosis of nanophthalmos include axial length ≤20 mm or hyperopia ≥+8.00 D.[14] The relationship between nanophthalmos and uveal effusion is a well-described entity. In a normal eye, fluid and protein drain from the choroid through the vortex veins, transscleral hydrostatic diffusion, and flow through scleral emissary channels. Scleral composition is a major factor in this process. Scleral tissue is made up of collagen and elastic fibers with interspersed proteoglycans. In nanophthalmic eyes, increased scleral thickness, irregular arrangement of collagen fibers, and increased deposition of proteoglycans result in compression of the vortex veins and impedance of macromolecule permeability. This leads to reduced hydraulic conductivity and accumulation of

protein in the suprachoroidal space with a subsequent increase in osmotic gradient, further favoring fluid accumulation.[3,6] Nanophthalmos was the presumed risk factor for uveal effusion in three eyes in our series. Uyama et al[3] divided eyes with UES into three groups, Types 1 through 3. Type 1 included nanophthalmic eyes, Type 2 included non-nanophthalmic eyes with thick sclera, and Type 3 included a nonnanophthalmic eye without scleral abnormalities.[3] They performed subscleral sclerectomies at two sites, the inferotemporal and inferonasal quadrants, in 17 eyes. The subscleral sclerectomies consisted of a twothirds thickness scleral flap, measuring 4 mm · 5 mm, with excision of the remaining sclera, measuring 3 mm · 4 mm, and exposure of the choroid. They found that this surgical technique was effective for UES Types 1 and 2, but not effective for Type 3. According to this grading system, Case four would be classified as Type 3, although we did find that surgical intervention with PTSs and MMC was effective. Mitomycin C is a well-known medication used to prevent scleral scarring after scleral surgery, such as trabeculectomy and deep sclerectomy. Mitomycin C can be used to reduce scarring of the sclerectomy bed, and some have reported successful treatment with resolution of choroidal and retinal detachments in eyes receiving scleral surgery supplemented with MMC.[9,10,15] However, we noted success with the use of adjuvant MMC in Case 4, but not in Case 2. Despite this, MMC will continue to remain in our armamentarium against uveal effusion. Sabrosa et al[9] described success using a technique involving PTSs with punch sclerostomies and MMC, and suggested that early intervention with radical full-thickness sclerectomies leads to the best results in patients with nanophthalmos and UES. Additionally, they described a scleral punch method using the Kelly punch instead of a scalpel, as they believed it was safer for a number of reasons, including rounded design and more controlled use. In our series, we implemented a graded surgical approach, and only one eye required full-thickness sclerectomies for successful treatment. In Case 2, we performed punch sclerostomies with a Kelly punch, and found that this instrument allows for greater control and reduces the risk of choroidal hemorrhage. Vortex vein decompression is one of the oldest described surgical techniques for the management of UES, although it has become a less favored method, as isolation of the vortex veins is very complex, decompression is technically difficult, and there is a high risk of complications, including vein rupture and cauterization of the vessel.[8,12] Because scleral thinning procedures alone are successful in the treatment of UES, we no longer perform or recommend vortex vein decompression for UES. Because subretinal fluid drainage with external approach after PTS is associated with a substantial risk of subretinal hemorrhage compared with a routine detachment, especially given an already thickened and engorged choroid, it has not previously been described. Schneiderman et al[16] described internal drainage of subretinal fluid performed in conjunction with pars plana vitrectomy and PTS. The authors proposed that as the external drainage approach is riskier, an internal approach might be preferred. Although the risk of choroidal and subretinal hemorrhage must be considered and discussed with the patient before surgery, we found that the external approach can be safely performed with careful surgical planning.

While UES can be a devastating disorder, recalcitrant to treatment, and recurrent even after successful treatment, our described surgical techniques were effective in preventing and treating uveal effusions. Given the significant visual consequences of chronic and recurrent subretinal fluid, one must weigh the potential morbidity associated with more aggressive surgical approaches against the risks associated with recurrence and chronicity of the disease. As our understanding of UES progresses, we hope to be able to apply a more tailored surgical approach for patients. In our series, implementation of a step-wise approach to the surgical management of uveal effusions proved successful without complications, in all six eyes. When deciding which treatment modalities and surgical techniques are most appropriate for a patient, it is important to consider the underlying ophthalmic condition and apply a graded surgical approach.

Key words: choroidal detachment, nanophthalmos, scleral windows, sclerectomy, uveal effusion, uveal effusion syndrome.

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Correlation of Ganglion Cell Complex (GCC) and Retinal nerve fiber layer (RNFL) thickness in relation to Glycemic control and lipid profile in Diabetics and age matched normal

- Dr. Shivanna Kagathur,[1] Dr. Pooja B.[1]

[1] Department of Ophthalmology, JJM medical college, Davanagere,Karnataka

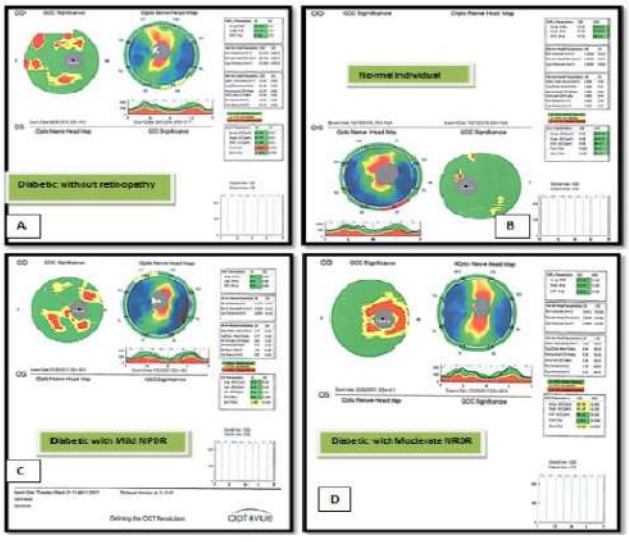
Abstract

Purpose: To evaluate the thickness of GCC layer and RNFL in diabetics with respect to duration of diabetes, HbA1c level and Lipid profile in comparison to age matched normal.**Methods**: Prospective study of 150 eyes of 150 patients. Patients were divided into 50 controls, 50 diabetic with diabetic retinopathy and 50 diabetic with no diabetic retinopathy changes. All the patients were evaluated using a standard SD OCT. Biochemical parameters-HbA1c and lipid profile were also evaluated.**Results:** Our study showed significant GCC thinning in diabetes which is mainly focal than diffuse and non-significant loss of RNFL. As the duration of diabetes increased there was a significant loss of GCC and RNFL. Increased HbA1c levels lead to non-significant thinning of GCC and RNFL. There was no significant correlation between altered lipid profile and OCT parameters.**Conclusion:** The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss. Hence OCT can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen.

Keywords: Diabetes, gCC, RNFL, HbA1c and lipid profile

Introduction

Diabetic retinopathy (DR) is one of the leading causes of blindness according to vision 2020 protocol.[1] Due to the large number of diabetic subjects, DR is likely to pose a public health burden in India. CURES Eye study showed that the major systemic risk factors for onset and progression of DR are duration of diabetes, degree of glycemic control and hyperlipidaemia.[2] Early detection of diabetic retinopathy is particularly essential for patients with diabetes mellitus because advanced diabetic eye disease is refractory. With advanced technologies, various phenomena that relate to retinal changes at retinal micro-vascular level have been reported in cases with no diabetic retinopathy changes.The RNFL forms the innermost neural layer of the retina and is composed of the large unmyelinated axons of ganglion cells. RNFL fibers originate from different locations of the retina and converge together in a unique pattern to form the optic nerve. The ganglion cell complex (GCC) is defined as the three innermost retinal layers: the nerve fiber layer, the ganglion cell layer, and the inner plexiform layer.[3] The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss and OCT can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen. Understanding of these retinal structural changes in early stages of diabetic retinopathy may provide information regarding progression (Figure 1).



Optical properties of the intraretinal layers may provide useful information to differentiate pathological from healthy eyes. It is known that diabetes leads to thinning of the retina preceding the onset of severe diabetic retinopathy, which is most possibly attributed to neurodegeneration.[4] So we decide to do this study to detect changes in the ganglion cell layer and RNFL of retina in diabetic and normal healthy subjects using SD OCT.

Methods

Prospective study of 150 eyes of 150 patients aged ≥ 18 years (Group 1;50 control, Group 2;50 diabetic with diabetic retinopathy and Group 3;50 diabetic with no diabetic retinopathy) were included in the study. The study was approved by the Institutional review board. Patients with glaucoma or those with intraocular pressure (IOP) >21mmHg in either eye, those showing evidence of visual field defects in either eye as detected using Humphrey visual field analyzer, hypertension, diabetic macular edema, high myopia, severe ocular trauma, refractive surgery and any high risk proliferative diabetic retinopathy condition altering the OCT examination (i.e. preretinal hemorrhages, vitreous traction retinal detachment/ combined retinal detachment), Any other retinal disorders affecting RNFL and GCC layers were excluded from the study. Informed consent was obtained from all the patients. Each patient was subjected to detailed history taking, followed by complete ophthalmic evaluation including Best corrected Vision assessment; Intraocular pressure, slit lamp examination, fundus evaluation using slit lamp biomicroscopy and indirect ophthalmoscope. One eye of each patient either OD/OS was included in the study.

GCC and retinal nerve fiber layer analysis was done by using OPTOVUE (RTVue100) OCT with software version 6.3.0.62.It was performed through dilated pupil and external fixation was used. ONH/GCC symmetry analysis was obtained.OCT was repeated when the obtained scans were not appropriate due to poor focusing or inadequate centration .The patient was excluded if repeat scans were unsatisfactory .Finally the selected OCT scans were analyzed, then retinal nerve fibre layer, ganglion cell complex, focal loss volume, global loss volume thickness values were obtained.5 ml of blood sample was obtained from all patients for Investigations (Glycemic status and Lipid profile)

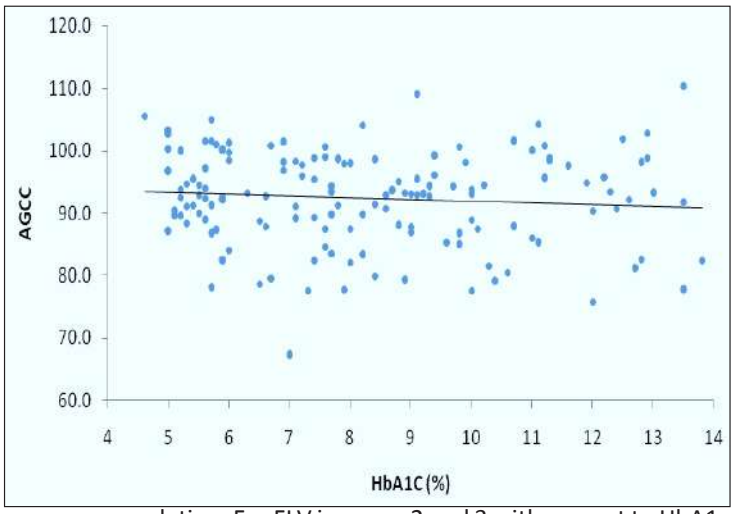
Results

Mean age was 57.3±12.7 in group 1, 58.6±12.1 in group 2 and 60.9±8.6 in group 3. The mean ratio between males to females is 19/31 in group 1, 27/23 in group 2 and 29/21 in group3. Mean HbA1c range was 5.37±0.42 in group 1, 9.36±2.27 in group 2 and 9.40±2.08 in group 3.On statistical analysis F (One Way ANOVA)= 48.25 and p-value of <0.001 was obtained, suggesting a statistically highly significant correlation. The mean triglyceride values were 183.6±97.5 in group 1, 235.3±131.0 in group 2 and 189.1±111.3 in group 3. On statistical analysis F (One Way ANOVA)= 3.10 and p value of 0.05 was obtained, suggesting a statistically significant correlation. A non-significant correlation was seen with F (One Way ANOVA)= 2.45 and p= 0.09, for HDL values in all the 3 groups . Over all LDL values in the 3 groups on statistical analysis obtained an F= 6.95 and p= 0.001, suggesting a statistically significant correlation. However Total Cholesterol mean values were 189.9±4.46 in group 1, 206.1±43.2 in group 2 and 170.2±41.9 in group 3. On statistical analysis F = 8.67 and P=0.00 was obtained, suggesting a statistically significant correlation. The mean values of VLDL and TC/HDL in all 3 groups on statistical analysis obtained a statistically significant correlation with p< 0.05.GCC and RNFL thickness measurements in all three groups are shown in table 1.

AGCC- Average GCC, **SGCC**-Superior GCC, **IGCC**-Inferior GCC, **FLV-** focal loss volume**, GLV**- Global loss volume, **ARNFL**- Average RNFL, **SRNFL**- Superior RNFL, **IRNFL**- Inferior RNFL ,**NS**- Not significant

Groups	AGCC	SGCC	IGCC	FLV	GLV	ARNFL	SRNFL	IRNFL
1	94.3±6.8	94.6±7.4	94.0±7.4	1.51±1.89	5.87±4.99	107.2±11.5	111.4±13.4	102.3±11.5
2	92.2±8.8	91.9±8.5	92.5±9.5	1.91±2.09	7.24±6.58	103.8±11.8	107.2±13.5	100.7±11.2
3	90.8±6.5	89.4±7.6	92.2±8.6	3.32±2.61	8.08±5.27	103.5±21.2	106.7±19.9	100.8±23.4
ANOVA F	2.93	5.39	0.67	9.17	1.90	0.91	1.34	0.15
P value	0.05 *	0.006 *	0.51, NS	0.00 **	0.15,NS	0.41,NS	0.27, NS	0.85,NS

For the two diabetic groups further sub analysis was done to analyze the relation between HbA1c range and OCT parameters. In group 2, AGCC mean values obtained with respective to HbA1c range (<6.0) was 91.9±3.1, (6.1-8.0) was 91.3±9.8, (8.1-10.0) was 92.3±8.4 and (>10.0) was 92.6±10.1. On statistical analysis, F=0.05 and p=0.98 was obtained suggesting a non-significant correlation. In group 3, AGCC mean values obtained with respective to HbA1c range (<6.0) was 87.0±4.2, (6.1-8.0) was 89.5±7.5, (8.1-10.0) was 91.8±4.6 and (>10.0) was 91.6±7.1. On statistical analysis, F=0.66 and p=0.59 was obtained suggesting a non-significant correlation. For FLV in group 2 and 3 with respect to HbA1c



range F=1.34, p=0.27 and F=0.81, p=0.50 was obtained suggesting a non-significant correlation. Global loss volume (GLV) in both the diabetic groups with respective to HbA1c range obtained F=0.46, p=0.46 in group 2 and F=0.0.81, p=0.81 in group 3 suggesting a non-significant correlation. The relation between Hb A1C and AGCC are shown in *Figure 2*. The ARNFL mean values with respective to HbA1c range in group 2 obtained F=0.08 and p=0.97 suggesting a non-significant correlation. But in group 3 on statistical analysis, F=5.26 and p=0.003 was obtained suggesting a significant correlation.

The relationship between Triglycerides and OCT findings were as follows: For AGCC with respect to TG range mean values for group 1 was 96.0±4.9 for (<150), 89.5±7.9 for (150-199) and 95.3±6.9 for (>200). On statistical analysis, F=4.05 and p=0.02 was obtained suggesting a significant correlation. But for the diabetic groups a non-significant correlation was obtained for the same with p > 0.05.In all the 3 groups FLV with respect to TG range showed a non-significant correlation with p>0.05.GLV with respect to TG range for group 1 was 4.52±3.79 for (<150), 9.40±6.52 for (150-199) and 5.26±4.37 for (>200). On statistical analysis, ANOVA F=4.12 and p=0.02 were obtained suggesting a significant correlation. However the diabetic groups showed a non-significant correlation with p>0.05. The mean values for ARNFL with respect to TG range in group 1 was 110.6±10.2 for (<150), 100.1±11.7 for (150-199) and 107.7±11.4 for (>200). On statistical analysis, ANOVA F=3.30 and p=0.05 were obtained suggesting a significant correlation. But the same relation in diabetics group was not significant (p > 0.05).The relationship between Total cholesterol (TC) and OCT findings were as follows. The mean values of AGCC with respect to TC range in group 1 was 95.8±6.6 for (<200), 90.1±7.5 for (200-239) and 95.3±4.2 for (>240). On statistical analysis, ANOVA F=3.04 was obtained and p=0.04 which suggested a significant correlation. But the diabetic groups showed a non significant correlation with p > 0.05.The mean values of FLV with respect to TC range in group 1 was 0.97± 1.23 for (<200), 2.76±2.60 for (200-239) and 1.56±1.99 for (> 240). On statistical analysis, ANOVA F=4.27 was obtained and p=0.02 which suggested a significant correlation. But in group 2 and 3 the correlation was non-significant (p > 0.05).The mean values of GLV with respect to TC range in all the groups had a non-significant correlation (p > 0.05). The mean values of ARNFL with respect to TC range in group 1 was 110.4±9.5 for (<200), 101.3±14.3 for (200-239) and 104.9±10.8 for (>240). On statistical analysis, ANOVA F=3.10 and p=0.05 was obtained which suggested a significant correlation. However in diabetic groups it showed a non-significant correlation (p > 0.05)

The relationship between LDL and OCT findings were as follows: Over all AGCC with respect to LDL range in all 3 groups suggested a non-significant correlation (p>0.05). For FLV with respect to LDL range mean values in group 1 was 1.03±1.20 for (<100), 1.04±1.44 for (100-129), 1.05±0.91 for (130-150) and 3.37±2.99 for (>150). On statistical analysis=5.02 and p=0.004 was obtained, which suggested a significant correlation. But among diabetic groups (2 and 3) non-significant correlation was obtained (p>0.05). GLV and ARNFL with respect to LDL range in all 3 groups showed a non-significant correlation with p value >0.05.

Relationship between duration of Diabetes and OCT findings are shown in table 2. Correlation analysis was done in order to access the relationship between OCT findings and selected biochemical parameters shown in table 3. There was an inverse relationship between HbA1c and AGCC/ARNFL layers showing as there is increase in HbA1c there will be decrease in the layer. However this relationship was not significant. Positive relationship was found between HbA1C and FLV/GLV showing as there is an increase in HbA1c there in an increase in FLV/GLV. No significant correlation was found between lipid profile and OCT parameters. Similar to HbA1c results duration of diabetes also found to be inversely related to AGCC and ARNFL and a positive relationship was present with respect to FLV /GLV .Relation between duration of Diabetes and AGCC shown in figure 3.

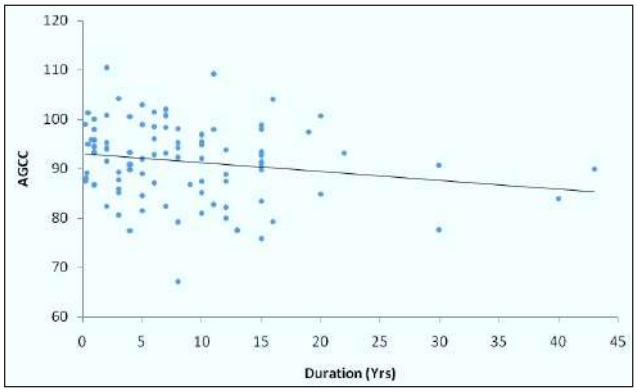
Table 2: Relationship between Duration of Diabetes and OCT findings

Duration (Yrs)	AGCC		FLV		GLV		ARNFL	
	G2	G3	G2	G3	G2	G3	G2	G3
< 5 yrs	92.3±6.9	93.8±6.7	1.57±1.40	1.48±1.34	6.90±4.92	4.11±3.23	106.9±10.5	107.9±15.4
5 - 10	92.2±9.8	91.2±6.5	1.32±1.71	3.68±.48	6.90±8.06	8.13±4.32	102.6±14.5	108.0±25.7
> 10 yrs	91.8±11.7	89.1±6.0	3.43±3.10	3.85±2.86	8.43±8.21	9.84±5.88	98.1±9.4	97.8±18.6
ANOVA F	0.02	1.99	4.32	3.41	0.22	4.66	2.38	1.43
P value	0.98,NS	0.15,NS	0.02*, S	0.04* S	0.80,NS	0.02*, S	0.10,NS	0.25,S
One Way ANOVA								
* P < 0.05, S								
P > 0.05, Not Sig.								

- significant, NS- Not significant

Table 3 -Correlation analysis between OCT findings and selected biochemical parameters and duration of Diabetes

Relationship with		AGCC	FLV	GLV	ARNFL
HbA1C	r	-0.09	0.25	0.14	-0.01
	P	0.28	0.003*	0.09	0.95
TGL	r	-0.02	-0.13	-0.02	0.09
	P	0.79	0.11	0.83	0.26
TC	r	0.03	-0.07	-0.03	0.07
	P	0.74	0.37	0.7	0.38
LDL	r	0.06	-0.05	0.01	0.05
	P	0.49	0.56	0.95	0.52
Duration of Diabetes.(Yrs)	r	-0.18	0.31	0.23	-0.38
	P	0.06*	0.002*	0.02*	0.00**
r: Pearson's Correlation Coefficient (-ve sign indicates inverse relationship)					
*P < 0.05,Sig					
** P< 0.001, HS					
P > 0.05, NS					



Discussion

Multiple studies have indicated that neuronal and vascular abnormalities are associated with the pathogenesis of early diabetic retinopathy.[5-9] Barber AJ et al, [6] showed retinal neuronal damage accompanies microvascular damage in patients with type 2 diabetes. Oshitari T et al,[8] in their immuno-histochemical studies of cross-sections of human retinas demonstrated an increase in expression of Bax, caspase-3 and caspase-9 in RGCs from diabetic patients, thus suggesting loss of some retinal ganglion cells via apoptosis. It is becoming increasingly evident that neuronal cells of the retina also are affected by diabetes, resulting in neuronal dysfunction and even degeneration of some neuronal cells. Retinal ganglion cells have been implicated in this pathology.[2]

Demir M et al[10] studied the RNFL and GCC thickness in patients with no DR, mild NPDR and moderate NPDR and healthy participants and concluded that there is a non significant loss of RNFL and GCC in patients with type 2 diabetes. Wei G et al, [11] concluded thickness values of GCL+IPL and OPL showed a significant decrease in DR eyes compared to controls. Dorothy SK Ng et al, [12] examined the association of diabetes and DR with retinal ganglion cell loss in Type 2 diabetes and age-gender matched controls without diabetes. They concluded that RGC loss is present in subjects with diabetes and no DR, and is progressive in moderate or severe DR. RGC neuronal damage in diabetes and DR can be clinically detected using OCT.

Asnaghi V et al,[13] concluded that the RNFL defect is common in patients with early DR. Chhablani J et al,[9] concluded average and minimum GCIPL showed significant thinning in diabetic subjects compared with controls in all stages of DR, especially involving the papillo-macular bundle. GCIPL thickness was similar between the diabetic groups. No relationship between GCIPL, RNFL thicknesses and duration of diabetes was present. Araszkiewicz A et al,[14] subjects with retinopathy had thinner para-foveal retina, reduced mean RNFL thickness, reduced inferior and nasal RNFL thickness, and reduced superior and inferior GCL. Significant correlations were found between duration of diabetes and nasal RNFL thickness and para-foveal retinal thickness. They noted significant RNFL thinning with increase in duration of diabetes mellitus. Asefzadeh B et al,[15] concluded that in subjects with no or mild DR, macular and foveal thickness is significantly thinner with longer duration of disease. They concluded that, this may reflect neurodegenerative changes in the diabetic retina. Araszkiewicz A et al, [14] significant correlations were found between duration of diabetes and nasal RNFL thickness and para-foveal retinal thickness. They noted significant RNFL thinning with increase in duration of diabetes mellitus. Asefzadeh B et al[15] also concluded there was a significant negative correlation between retinal thickness and diabetes duration in all macular quadrants. In our study duration of diabetes was found to be inversely related to AGCC and ARNFL and a positive relationship was present with respect to FLV /GLV

Zhu T et al,[16] macular GCC reduction occurred much earlier than peripapillary RNFL thinning in diabetic patients without retinopathy. Ng DS et al,[17] RGC loss is present in subjects with diabetes and no DR, and is progressive in moderate or severe DR. RGC neuronal damage in diabetes and DR can be clinically detected using OCT. Salvi L et al,[18] concluded that the GCC is significantly affected in patients with type 2 diabetes and SD-OCT might represent a useful tool to detect Diabetic polyneuropathy (DPN), but not DR in these individuals but in our study we did not evaluate for polyneuropathy. Dhasmana R et al,[19] neurodegeneration is seen as an early component of diabetic retinopathy. They also evaluated GCC and it showed statistically significant in diabetic patients creatinine levels showed a week negative correlation to the RNFL; however in our study we did not evaluate creatinine levels.

In our study we found that with respect to average ganglion cell complex mean values in group 1, group 2 and group 3 was 94.3±6.8, 92.2±8.8, 90.8±6.5 and On statistical analysis F (One Way ANOVA)= 2.93 and p=0.05 was obtained, suggesting a *statistically significant correlation*. The average RNFL mean values in group 1, group 2 and group 3 was 107.2±11.5, 103.8±11.8, 106.7±19.9 and On statistical analysis F (One Way ANOVA)= 0.91 and p=0.91 was obtained, suggesting a *statistically non-significant correlation*.

Hegazy AI et al,[20] FLV% was negatively correlated to the refraction and level of HbA1c (p=0.019 and 0.013 respectively) and positively correlated to BCVA in log MAR in diabetic group (p=0.004).They concluded that significant GCC thinning in diabetes predates retinal vasculopathy, which is mainly focal rather than diffuse. It has no preference to either the superior or inferior halves of the macula. Increase of myopic error is significantly accompanied with increased focal GCC loss. GCC loss is accompanied with increased C/D ratio in diabetic eyes. But we did not include high myopia in this study.

Srinivasan S et al,[21] Diabetic peripheral neuropathy is associated with abnormal GCC FLV at the macula, which is independent of diabetic retinopathy, age, sex, type of diabetes, duration of diabetes and HbA1c levels. An abnormality in GCC FLV is an independent predictor of diabetic peripheral neuropathy. However in our study we found that with respect to Focal loss volume mean values in group 1, group 2 and group 3 were 1.51±1.89, 1.91±2.09, 3.32±2.6 respectively. On statistical analysis F (One Way ANOVA) = 9.17 and p= 0.00 was obtained, suggesting a *statistically significant correlation*

Pekel E et al,[22]Diabetic patients without retinopathy have more binocular RNFL thickness asymmetry, higher cup to disc ratio, and thinner sectoral macular GCL+IPL when compared to healthy control and supports the statement that DM causes inner retinal neurodegenerative changes. But in our study we did not include ONH parameters.

Debadatta C et al, [23] aimed to study any correlation of RNFLT with blood glucose parameters. RNFLT showed significant negative correlation with blood glucose parameters. Especially for HbA1C, this correlation was high in all quadrants around optic nerve head. Further studies will be needed to elucidate the relation of other blood parameters such as cholesterol with retinal thickness in diabetes. In our study lipid profile was done and compared to the retinal thickness. In our study no correlation was found between OCT parameters and lipid profile. In our study in group 2 and 3 the AGCC with respect to HbA1c range obtained F=0.05,p=0.98 and F=0.66,p=0.59 respectively suggesting a non-significant correlation. However the ARNFL values with respective to HbA1c range in group 2 obtained F=0.08 and p=0.97 suggesting a non-significant correlation. But in group 3 on statistical analysis for the same relation, F=5.26 and p=0.003 was obtained suggesting a *significant correlation*.

Gundogan FC et al,[24] Type 1 diabetic patients without clinically diagnosed DR had neurodegeneration in the inner retinal layers compared with healthy controls. We did not consider type 1 diabetes in our study. El-Fayoumi D et al,[25] concluded that thinning of the RNFL and GCC in children with T1DM with no DR compared to healthy controls suggests that neurodegenerative changes occur in the absence of vascular changes. It also shows that neurodegeneration is not related to disease duration, onset, or control.

In conclusion, as the duration of diabetes increases there was a significant loss of GCC and RNFL. With poor glycemic controls (increased HbA1c) thinning of GCC was non-significant and the loss was more focal (FLV) than diffuse (GLV). With poor glycemic control decrease in RNFL thickness was non-significant. There was no significant correlation between altered lipid profile with respect to GCC and RNFL. The results of our study are similar to earlier studies. However, unlike other studies we did not evaluate the correlation between higher grades of retinopathy i.e. severe NPDR and PDR, increased axial length and certain systemic correlates like diabetic neuropathy and diabetic nephropathy. The GCC and RNFL loss in diabetics could be an early indicator of neuronal loss. Hence OCT can be a useful non-invasive tool for early detection of neuronal loss even before retinopathy changes are seen. Multiple studies with larger population and longer follow ups are needed to assess the efficacy and importance of this outcome.

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Conflicts of Interest- None

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Ocular manifestations of Rickettsial disease

- Dr. Kruthika Singnal MS[1], Dr Poornima MS[2], Dr Suresh Rajappa MS[3]

[1]Department of Ophthalmology, JJM Medical College, Davanagere.

Abstract

Purpose-

To study the ocular manifestations and its management in spotted fever and typhus group of rickettsial disease.

Methods-

Cross sectional study of 50 patients with serologically confirmed Rickettsial disease were included. In all patients detailed history, investigations and treatment details were collected and they underwent complete ophthalmic evaluation including measurement of best corrected visual acuity, anterior segment examination and dilated fundus examination.

Results-

Mean age of the patients was 12.5 ± 8.99 years. Of 50 patients, 27(54%) had ocular involvement. Bilateral involvement was seen in 10 patients. Most of the patients had no ocular symptoms. Ocular findings included, Retinal vasculitis 6(22.22%); macular edema 4(14.81%); vasculitis with macular edema 1(3.7%); Retinitis 7(25.92%); Papilloedema 6(22.22%);Papilloedema with 6th cranial nerve palsy 1(3.7%);Isolated 6th cranial nerve palsy (3.7%) and optic neuritis 1(3.7%). Ocular involvement was more common in double antigen group (68%) than spotted fever group (50%) or Scrub typhus group (21%). Ocular involvement was seen in 94% of the patients with CNS involvement. All cases received systemic antibiotics. Optic neuritis case received systemic steroids along with antibiotics.

Conclusion-

Rickettsioses patients can have ocular manifestations and CNS involvement during acute illness. Posterior segment involvement was more common and ocular involvement was more common in double antigen positive group than scrub typhus

Key words- Ocular manifestations, Rickettsial disease

Introduction

Rickettsioses are worldwide distributed zoonoses caused by obligate intracellular small gram-negative bacteria belonging to the genus Rickettsia. Most of them are transmitted by the bite of contaminated arthropods, such as ticks, mites. The majority of rickettsial organisms are known to invade small blood vessels causing endothelial injury and tissue necrosis, with subsequent development of host mononuclear-cell tissue response and stimulation of coagulation process, resulting in a systemic edematous and occlusive vasculitis.[1]

Rickettsial agents are classified into three major categories: the spotted fever group, the typhus group, and the scrub typhus [1].Treatment of these infections is highly effective in early course of the disease but it is extremely difficult to make a diagnosis at this stage due to low index of suspicion, non-specificity of signs and symptoms and absence of low cost, rapid and widely available diagnostic test. Diagnosis of rickettsial disease is usually based on clinical features confirmed by positive serologic testing. In countries like India, where PCR and IFA are not commonly available, properly performed paired serological tests like weil felix and ELISA have high positive predictive value. Weil-Felix test still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease.[2]

Systemic involvement is characterized by triad of high fever, headache and general malaise, and skin rash. Ocular involvement is common in patients with rickettsioses, but since it is frequently asymptomatic and self-limited, it may be easily overlooked [,3,4] However, rickettsial ocular disease may be associated with ocular complaints, such as decreased vision, floaters, redness or scotomas. Ocular findings include conjunctivitis, keratitis, anterior uveitis, panuveitis, retinitis, retinal vascular changes and optic nerve involvement. Retinitis, retinal vascular involvement and optic disc changes are the most common ocular findings. Ocular involvement associated with rickettsial infection usually has a self limited course, but, it can result in persistent visual impairment. Though rickettsial disease is common, there is paucity of reports of ocular manifestations in rickettsia. Moreover, rickettsial sub-types and their ocular involvement have not been studied. We report ocular manifestations, treatment given, and visual outcome in patients with systemic rickettsial disease who attended

our tertiary eye care center. To the best of our knowledge, this is the first incidence of study on ocular manifestations in various subtypes of rickettsiosis being reported as a cluster from India.

Methods

Cross sectional study conducted on 50 patients with Rickettsial disease. Study was approved by Institutional review board. All patients with the clinical signs suggestive of rickettsial disease with Weil felix test positive (Titre>1:80) were included in the study. Serologically negative cases were excluded from the study. Informed and written consent was obtained from each selected patient or from their parents or near relatives. The demographic profile of serologically proven cases of rickettsial disease was collected. Detailed history was taken and the clinical details were entered in to standard prepared proforma. In all patients detailed history, details of systemic examination, investigations and treatment details were collected. All patients had a negative dengue serology and a negative human immunodeficiency virus (HIV) test which was done to rule out simulating retinitis. WFT interpretation and rickettsial sub-classification was done according to Table 1.

Table 1: WEIL FELIX test (WFT) interpretation

	OX 19	OX 2	OX K
Epidemic typhus	++++	+	0
Brill Zinsser disease	++++	+	0
Murine typhus	++++	+	0
Scrub typhus	0	0	+++
Rocky mountain spotted fever	++++	+	0
Other tick borne typhus	+	++++	0
Indian tick typhus	+	++++	0

Visual acuity was assessed at bedside for bedridden patients. For ambulatory patients, visual acuity was assessed with and without correction using Snellen's chart. Thorough pupillary examination was carried out for pupillary reactions. Patient was assessed for ocular alignment and extraocular movements. Extraocular movements assessed were ductions, versions, convergence, saccades and pursuits. Anterior segment examination was done by bright flash light or slit lamp depending upon the status of the patient. Dilated fundus examination was done using slit lamp biomicroscopy and indirect ophthalmoscopy. Serial follow up examination was performed in patients with posterior segment eye changes. Intraocular pressure was recorded using Goldmann applanation tonometer/Rebound tonometer wherever necessary.FFA and OCT examination was done in relevant cases and co operative children. Diplopia charting was done whenever the patient complains of diplopia. Any ocular manifestation which required treatment was treated as per standard medical practices.

Statistical analysis was carried out using IBM SPSS version 20 for Windows. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi Square test with continuity correction for 2 x 2 tables and Fisher's exact test for all 2 x 2 tables where P value of chi square test was not valid due to small counts. Adjacent row data of more than 2 x 2 tables was pooled and chi square test reapplied in case of more than 20% cells having expected count less than 5.Age as a quantitative data was represented using mean & SD.

Results

Mean age of the patients was 12.5 ± 8.99 years. The total number of patients studied was 50. Out of which, 27 were males (54%) and 23 were females (46%). Among 50 patients, 26 patients had systemic findings. Among them 8 (30.77%) had encephalitis; 6(23.07%) had hepatomegaly ; 3(11.53%) had hepatospleenomegaly ; 6 (23.07%) had meningitis ;1(3.85%) had meningoencephalitis ; 1(3.85%) had spleenomegaly ; and 1(3.85%) had multiple organ involvement .

Two patients (4%) were positive to OX 2 only; 14 (28%) patients were positive for OX K only; 29(58%) patients were positive for OX 19 and OX 2; 4(8%) patients were positive for both OX 2 and OX K., and 1(2%) patient was positive for both OXK and OX19. Single antigen positivity was seen in 16(32%) patients and the remaining 34(68%) patients were positive for two antigens (Double antigen group).

Best corrected visual acuity (BCVA) ranged from 6/6 to 1/60.Thirty nine patients (78%) had normal vision, 6(12%) had decreased vision and for 5(10%) patients vision could not be assessed due to poor systemic status. Twenty seven patients (54%) had ocular manifestations. Out of 27 patients, 17 (63%) patients had unilateral ocular involvement, 6(22.22%) had retinal vasculitis ; 4(14.81%) had macular edema ; 1(3.7%) had vasulitis with macular edema ; 7(25.92%) had Retinitis;6(22.22%) had papilloedema ; 1(3.7%) had papilloedema with 6th cranial nerve palsy ;1(3.7%) had 6th cranial nerve palsy and 1(3.7%) had optic neuritis(Figure 1). Central nervous system involvement was seen in 16 cases, out of which 15(94%) had ocular findings. Other systems were involved in 10 cases, out of which 5(50%) had ocular findings.

Two cases of spotted fever group and 14 cases of scrub typhus group had normal vision. In Double antigen group, out of 34 cases; 23(68%) had normal vision; 6(17%) had decreased vision and 5(15%) cases vision could not assess due to poor systemic status. Ocular manifestations were seen in 1 spotted fever, 3 scrub typhus and 23 double antigen group patients (Figure 2). Among the patients who had ocular manifestations, in spotted fever group, 1 patient (100%) had papilloedema .In Scrub typhus group, 1 patient (33.33%) had retinal vasculitis; 1(33.33%) patient

had Retinitis; 1(33.33%) patient had 6th CN palsy. In double antigen group, 23 patients had ocular manifestations, among them 5(22%) patients had vasculitis ; 4(18%) had macular edema ; 1(4%) had vasculitis with macular edema ; 6(26%) had retinitis ; 5(22%) had papilloedema ; 1(4%) had papilloedema with 6th CN palsy(Figure3); 1(4%) had 6th CN palsy and 1(4%) had optic neuritis. Fundus fluorescein angiography (FFA) in posterior segment cases showed early hypo fluorescence corresponding to retinitis patches. These turned gradually hyper fluorescent at the border of the retinitis lesions. Leakage was seen in late phase. Macula showed no leakage. Patients aged more than eight were treated with tablet Doxycycline and chidren less than eight years were treated with intravenous azithromycin. Topical steroid were used in case of AC flare/cells. Visual acuity improved in all patients with final follow up at 6 months (range 6/6 to 6/18). Optic neuritis case received systemic steroids along with antibiotics.

Figure 1- Distribution of patients according to ocular manifestations

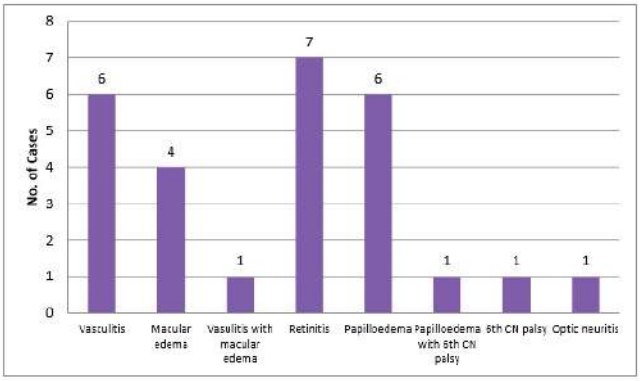


Figure 2-Posterior segment manifestations of Rickettsia;
2A- Multifocal Retinitis;
2B- Neuoretinits with macular edema;
2C- Juxtapapillary retinitis with hemorrhage,
2D- Retinal vasculitis with macular edema

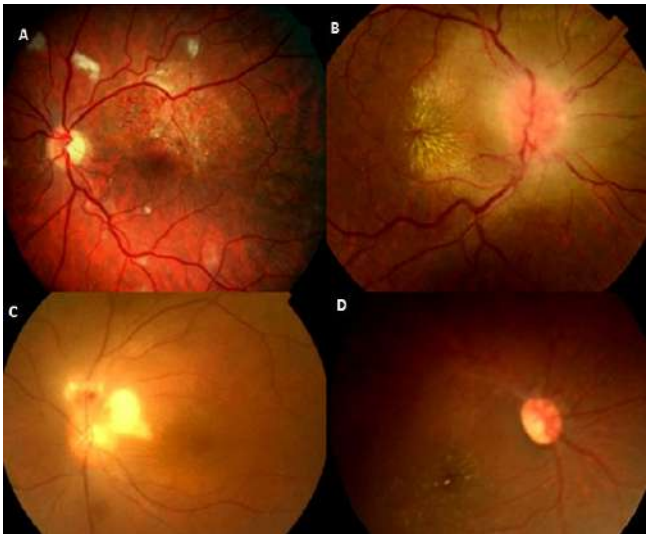
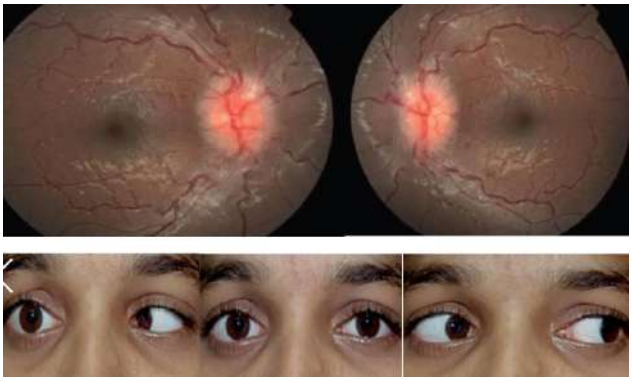


Figure 3- Papilloedema with sixth cranial nerve palsy



Discussion

Rickettsial disease is endemic in many parts of India.In a ten year study by Dasari et al,[5] ten out of eleven outbreaks were due to scrub typhus and one was due to spotted fever. All patients in this study had positive Weil-Felix serology with titer value of ≥1:80.As per Issac et al titre. [6] value of 1:80 has sensitivity of 30%, specificity and positive predictive value were 100%, thus to avoid false positive WFT, cut off value of titre 1:80 was considered in this study, but due to low sensitivity the cases might be missed.

Out of 50 patients, 2(4%) patients were positive to OX 2 antigen only suggestive of Spotted fever group ; 14 (28%) patients were positive for OX K antigen only suggestive of Scrub typhus .34(68%) patients were positive for two antigens and they were included in double antigen group. These 34 patients cannot be included in any particular subtype of rickettsia, unless newer molecular methods are used. 29(58%) patients were positive for OX 19 and OX 2 antigen; 4(8%) patients were positive for both OX 2 and OX K antigen, and 1(2%) patient was positive for both OX 19 and OX K antigen.

In our study, most of the patients were asymptomatic which might be due to the pediatric age group of the affected patients and associated predominant systemic illness. Alio J et al[3] study and Khairallah M et al[7] study reported that ocular involvement in rickettsioses is frequently asymptomatic which is similar to our observation. In our study 27(54%) patients had ocular manifestations. In the study done by Khairallah M et al [8], 68% had ocular involvement which is also almost similar to our study. In the study done by Khairallah M et al,[7] 83% had posterior segment involvement. In the study done by Khairallah M et al [7] 89% had ocular involvement. In our study, Total 27 patients had ocular findings. Unilateral ocular involvement was seen in 17(63%) patients and bilateral in 10(37%).Out of which 6 (22.22%) had retinal vasculitis ; 4(14.81%) had macular edema ; 1(3.7%) had vasulitis with macular edema ; 7(25.92%) had Retinitis;6(22.22%) had papilloedema ; 1(3.7%) had papilloedema with 6th cranial nerve palsy ;1(3.7%) had 6th cranial nerve palsy and 1(3.7%) had optic

neuritis. In the study done by Khairallah M et al,[7] 20% had unilateral and 80% bilateral ocular involvement; out of which 48.3% had retinal vasculitis , 30% had retinitis , 1.3 % had cystoid macular edema , 1.3% had optic disc edema. In the study done by Khairallah M et al,[8] 22% had unilateral and 78% had bilateral ocular involvement, out of which 42.5% had retinitis, 21.3% had vascular sheathing, 2.1% had macular edema and 4.3% had optic disc edema. Most of the retinal changes are detected during 10th to 17th day of the illness. In our study we did single examination and that during acute illness, and FFA could not be done in few children due to poor systemic status which might be the reason for less fundus findings and less bilateral ocular involvement as compared to other studies.

In our study 16 patients had CNS involvement, out of which 15(94%) had ocular findings. Other systems were involved in 10 cases, out of which 5(50%) had ocular findings its comparable to other studies.[3] In double antigen group, which we were not able to classify patients into any particular rickettsial subtype that is spotted fever group or typhus fever group, ocular involvement was more common in this group (74%) than scrub typhus (21%). Kawali A et al study[10] reported Indian tick typhus and epidemic typhus could be common causes of Rickettsial retinitis as compared to scrub typhus in India which is similar to our observation.

In our study, all cases received systemic Doxycycline and supportive treatment accordingly. Optic neuritis case received systemic steroids along with antibiotics. The role of antibiotics and steroids on the course of posterior segment disease is unknown. All cases showed good systemic clinical response to Doxycycline which is similar to other studies, Kumar et al[11] has demonstrated remarkable response to doxycycline and this response has been used as a diagnostic test. Reddy et al[12] reported complete recovery on treatment with Doxycycline and Azithromycin

External examination finding showed no eschar or nystagmus as compared to finding by by Scheie et al.[13] Rest of the external examination findings was similar. The posterior segment finding in our patient showed multifocal retinitis serous macular detachment with macular star exudates and optic disc involvement in the form of disc edema and disc leakage. These finding were similar to a study by Balasundaram et al[14] that showed all 12 patients (21 eyes) presented with visual impairment ranging between (20/2000–20/30), multifocal retinitis, and 16/21 eyes had serous macular detachment with macular star exudates and optic disc involvement as evidenced by disc edema, and disc leakage on FFA was seen in 7/21 eyes. Retinal vascular sheathing adjacent to the lesions was noted in 7/21 eyes.

In another similar study by Kahloun et al,[15] rickettsial disease leading to visual loss was studies in 16 eyes of 14 patients. Retinitis was observed in 14/16 eyes, serous macular detachment in 11/14 eyes, and optic neuropathy in 7/16 eyes.(16) A study by Khairallah et al,[7] showed less profound finding with white retinal lesions were seen in 18/60 patients, focal vessel sheathing in 5/60 patients, serous retinal detachment in 3/60 patients, macular star in 2/60 patients, and optic disc edema in one patient. The finding in Rickettsial disease is due to vasculitis leading to microvascular leakage, edema, tissue hypoperfusion, and end-organ ischemic injury.[3] Retinal injury is predominantly immune mediated with deposition of immune complexes and inflammatory cells in the retina may lead formation of white infiltrates. Diagnosis of Rickettsial disease is difficult and high index of suspicion is needed.

Study has certain limitations, sample size was small, and our cases were probable rickettsial disease based upon Weil-Felix test. Confirmatory tests like immunofluorescence assay (IFA) or immunoperoxidase assay (IPA) could not be done due to non-availablity, WFT has low sensitivity and some cases were two antigens positive which we could not classify into rickettsial subtypes.

In conclusion, more than half of the patients with Rickettsioses can have ocular manifestations during acute illness. Most of the patients had Posterior segment involvement with Retinitis, retinal vascular lesions, macular edema and optic nerve involvement. Rickettsioses with CNS involvement will invariably have ocular involvement. Ocular involvement is more common in double antigen positive group than scrub typhus. All cases showed good clinical response to Doxycycline and it remains the treatment of choice; however specific antibiotic and anti-inflammatory therapy may be required for the more severe vision threatening ophthalmic manifestations of the disease. A systematic ophthalmologic examination and mainly dilated fundus examination should be a part of the routine evaluation of any patient who presents with fever and/rash living in endemic area. Typical ocular findings, may help in the early diagnosis of rickettsioses while serologic test is pending, which allows an early initiation of appropriate therapy.

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Non stick IOL fixation- No flap, No glue, No suture

- Dr. Sunil Ganekal[1]

[1]Department of Ophthalmology, Davangere Netralaya, Davangere

Abstract

Purpose:

To assess the outcome, complications and its predictors in novel modified Sutureless-glueless flapless Scleral fixated IOL.

Methods:

Prospective study of 86 eyes of 74 patients who underwent sutureless glueless flapless scleral fixated IOL from June 2016 to March 2019. All patients underwent standard scleral fixated IOL without sutures or glue. Pre operative best corrected visual acuity (BCVA) and intraocular pressure. Horizontal corneal white to white (hWTW) diameter and axial length were assessed. All patients were followed up on day 1, 1 month, 3 months and 6 months. All patients had a minimum follow-up of 6 months. Postoperative BCVA, intraocular pressure, IOL centration and IOL-related complications were noted including tilt, decentration, dislocation, haptic extrusion, and optic capture.

Results:

Mean age was 66 ± 13.4 years. 86 eyes of 74 patients with aphakia, subluxated IOL and subluxated crystalline lens were included in the study. The mean preoperative BCVA was 1.21±2.8 (Log MAR). The mean post operative BCVA at 6 months was 0.34±0.21 (Log MAR).Significant improvement in mean BCVA at 6 months after the procedure (p=0.011). From the final analysis 10 eyes were excluded for insufficient follow-up, missing data, or concomitant surgery. There were 6 eyes excluded for technique modification, and 2 eyes for isolated haptic erosion from the scleral tunnel without lens malposition. From our final analysis of 68 eyes, 8 eyes (12%) developed complications of the IOL. Of these, 3 (38%) eyes underwent surgical intervention. Patients with large hWTW experienced significantly higher rate of complications (p=0.04). Longer axial length was not predictive of higher complication rate (p=0.08).

Conclusions:

Suture or glue is not an absolute must for scleral fixation of an IOL. Sutureless glueless flapless scleral fixation of IOL is a safe surgical option in eyes without capsular support with fewer complications, stable IOL, reduced surgical time, shorter learning curve, good refractive outcome and without any suture or glue related complications.

Keywords - Sutureless glueless flapless scleral fixated IOL, Outcome, Complications

Introduction

In the absence of adequate capsular support/ Apahkia for posterior capsular or ciliary sulcus intraocular lens (IOL) implantation, there are several options for fixating the lens, including IOL placement in the anterior chamber, or in the ciliary sulcus with fixation to the iris or sclera.[1] Each surgical technique has its advantages and may be associated with technique related complications.[2-4] Agarwal's glue-assisted posterior chamber IOL implantation technique was first described in December 2007,[5] and was a modification of Gabor and Pavilidis' original sutureless fixation technique. [6] While the technique has proven to have excellent results, short term and long-term complications may occur. [7,8] Hence we describe a novel modified technique of sutureless glueless flapless scleral fixated IOL, which avoids the complications associate with sutured scleral IOL and Glued IOL. We have observed a pattern in which mechanical complications following glued scleral fixated IOLs seem to occur more frequently in eyes with larger horizontal white to-white (hWTW) and increased axial length measurements, presumably due to a longer ciliary sulcus distance.[9] We decided to study the role of these anatomical predictors in our modified sutureless glueless flapless scleral fixated IOL.

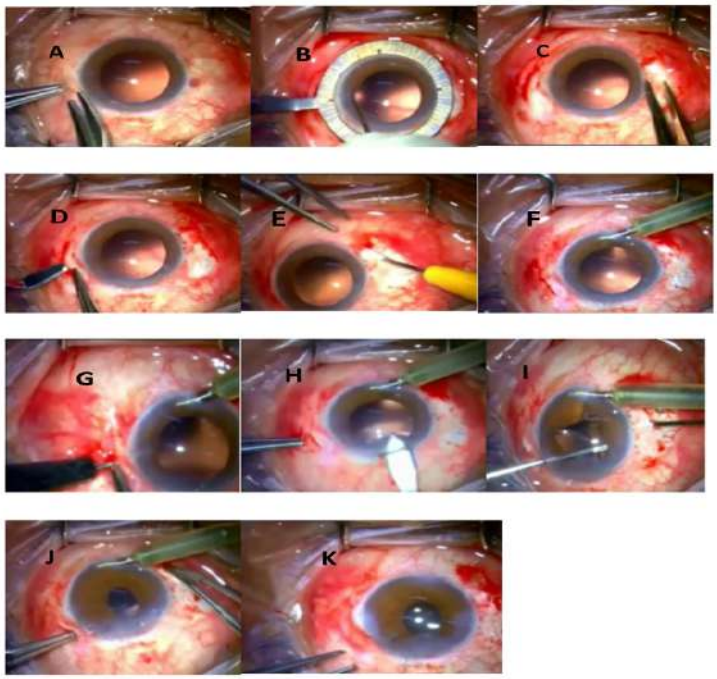
Methods

Prospective study of 86 eyes of 74 patients from June 2016 to March 2019. All patients underwent sutureless glueless flapless scleral fixated IOL. Study protocol was approved by the institutional review committee, and the study was performed in accordance to the tenets of Declaration of Helsinki. Informed consent was obtained from all the patients. All patients had a minimum follow-up of 6 months .Preoperative variables collected included demographics, date of surgery, surgeon, laterality, time from original IOL surgery to any secondary surgery, original IOL model and power, and pre-existing ocular co-morbitidies. Best-corrected final visual

acuity (BCVA) with a Log MAR chart as well as improvement or worsening from preoperative vision was recorded. The axial length (AL) , hWTW, corneal astigmatism were recorded from the IOLMaster™ version 700 (Carl Zeiss Meditec, Oberkochen, Germany).Operative variables recorded included IOL implant model (Sensar AR40e IOL; three piece hydrophobic monofocal),IOL power, surgeon, preoperative diagnosis, and intraoperative and postoperative surgical complications including IOL related and other vision-threatening complications requiring additional medical or surgical intervention.. All eyes that experienced complications of the implanted IOL were noted .Optic tilt of the IOL was identified by slit lamp examination, ultrasound biomicroscopy or Anterior segment OCT.IOL. Subluxation (defined as a partial displacement of the IOL) and/or IOL dislocation (defined as an IOL which was completely dislocated into the vitreous cavity away from the visual axis) were also recorded .All patients underwent sutureless-glueless flapless scleral fixated IOL.

Surgical technique (Figure 1A-1K)

Preoperative pupil centration marking was done under topical anesthesia. Surgery was done under peribulbar anesthesia.Limited peritomy done in the horizontal meridian on either side of the limbus(1A),0 and 180 degree horizontal marking done with 26 gauge needle(1B),after cauterizing the surface bleeders marking was done 2 mm from the limbus(1C),Partial thickness groove made 2 mm from limbus with the help of a scalpel blade and crescent knife(1D),in continuity with groove partial thickness scleral pockets are done with 1mm bent keratome for insertion of externalized haptics(1E),Anterior chamber maintainer was placed at 6 o'clock limbus(1F),scleral entry was made with 23 gauge trocar in the line of groove along horizontal meridian(1G),clear corneal entry done into anterior chamber(1H),anterior vitrectomy was done ,three piece monofocal hydrophobic IOL was injected into the anterior chamber, Externalization of haptics was done with hand shake technique(1I),externalized haptics were tucked into scleral pockets(1J),conjunctiva closed with cauterization, well centered IOL noted at the conclusion(1K). We excluded 6 eyes with technique modifications, such as suture of the haptics to the sclera. Postoperatively, each eye was also examined in the dilated state to assess if tilt or malposition was evident. We defined a large horizontal white-to-white distance as >12 mm, and longer axial length as >26mm, which are consistent with other reports in the literature.[9,10]Statistical analyses were performed using Microsoft excel to assess for statistical significance using the fishers exact T-test (two-tailed test with unequal variance) and the chi-square test. Values less than 0.05 were determined to be statistically significant.



Results

Mean age was 66 ± 13.4 years .There were 86 eyes of 74 patients who underwent sutureless glueless flapless scleral fixated IOL procedures performed between June 2016 and March 2019. There were 58 male and 16 female patients. The preoperative diagnoses for requiring secondary scleral fixated IOL surgery in our study group are listed in Table 1. The mean preoperative BCVA was 1.21±2.8 (Log MAR). The mean post operative BCVA at 6 months was 0.34±0.21 (Log MAR).Significant improvement in mean BCVA at 6 months after the procedure (p=0.011). Postoperatively, the mean spherical refraction was −0.040 ± 1.06D (range—1.75 D to +1.25 D), with a mean total astigmatism of −0.42 ± 1.20 D (range −2.00 to +2.00 D), a mean corneal astigmatism of −0.14 ± 1.24 D (range −1.75 to +2.0 D), and a mean spherical refractive equivalent of −0.32 ± 1.36 D. The mean difference between total and corneal astigmatism in these eyes was −0.06 ± 0.84 D (range −1.50 to +2.00 D), which may indicate that the IOL-induced astigmatism was minimal. We excluded 6 eyes that underwent additional concomitant ocular procedures such as corneal transplantation or glaucoma surgery. An additional 4 eyes had < 6 months follow-up hence excluded. We also excluded 6 eyes with technique modifications such as suture fixation of the haptics, as well as 2 eyes with isolated haptic slippage from the scleral tunnel without subsequent IOL malposition. Of the remaining 68 eyes, 6 eyes (9%) developed complications of the IOL. The most common IOL complications were optic tilt 2 eyes, subluxation 1 eyes, and optic capture in 1 eye. Of these eyes with IOL complications, 1 eye was surgically corrected, and none of the eyes underwent more than one corrective procedure. The most common reasons for surgical intervention were subluxation or tilt. UBM measured mean vertical tilt values were 0.22 ± 0.19 mm and the mean horizontal tilt values were 0.25 ± 0.16 mm. One eye with optic capture was treated in the office with dilation resulting in resolution of the optic capture. More than >50% of complications occurred in the

early postoperative period (within 6 weeks after the IOL procedure).Other early complications like hyphema, corneal striae and anterior chamber reaction were seen in 3 eyes. 2 eyes and 2 eyes respectively and all the eyes recovered with topical medications. None of the eyes had post-operative posterior segment complications except for vitreous hemorrhage in 2 eyes which resolve spontaneously over a period of 2 weeks. The mean pre-operative intraocular pressure was 13.8±2.9mm Hg. Seven eyes had raised intraocular pressure and were treated with topical anti glaucoma medication, average post operative intraocular pressure was 14.5±3.8 mm Hg. Patients with larger hWTW (>12mm) experienced significantly more complications (44%, p=0.05), and there was an increase in complication rate with increasing hWTW .There were 8 eyes with an axial length >26mm. Of these, the complication rate was 28%. Of the remaining 60 eyes with AL<26mm, the complication rate was only 22% (p=0.08). A total of 62 eyes (91%) achieved the same or better vision than preoperatively (p=0.001).

Figure 2- Pre operative subluxated IOL capsular bag complex and post-operative well centered IOL

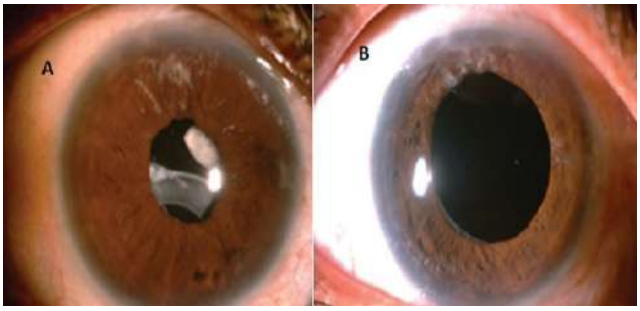


Figure 3- hWTW VS IOL complications

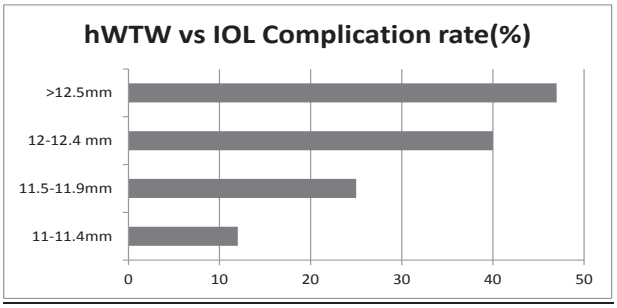


Table 1- characteristic, Indications, outcome and complications in study patients

characteristics	(n=68)
Age (years)	66 ± 13.4 years
Male:Female	58:16
Preoperative BCVA (mean Log MAR)	1.21±2.8
Mean Axial Length (mm)	24.2± 1.2 mm
Mean hWTW (mm)	11.9±1.3 mm
Mean pre-operative IOP	13.8±2.9mm Hg
Mean post-operative IOP	14.5±3.8 mm Hg
Etiology for secondary scleral fixated IOL	
IOL subluxation - Late endocapsular (Trauma/Pseudoexfoliatrion)	11(16%)
IOL subluxation - After previous secondary fixation	4 (6%)
ACIOL Exchange	7 (10%)
Subluxated crystalline lens	8 (12%)
Aphakia requiring secondary IOL	38 (54%)
Post-operative BCVA (mean Log MAR)	0.34±0.21
Mean post-operative astigmatism	−0.06 ± 0.84 D
Time from first surgery to IOL (years)	4.5± 1.2
Complications (Number of eyes)	
Self resolving Hyphema	3 (5%)
Corneal striae	2 (3%)
Raised Intraocular pressure	7 (!0%)
Anterior chamber reaction	2 (3%)
IOL tilt	2 (3%)
IOL Subluxation	1 (1%)
Optic capture	1 (1%)

Discussion

In the absence of adequate capsular support for IOL implantation, there are numerous options for secondary lens fixation. Scleral fixation provides an additional alternative to anterior chamber, iris fixated, and trans scleral sutured IOL techniques and allows the surgeon to place the lens posterior to the iris in the sulcus and avoid the iris related complications.[1-5,7] In general, the IOL centration appears excellent and it is presumed that the thickness and strength of haptic fixation will be less likely to suffer the mechanical breakdown seen in suture techniques over time. The short-term results of this technique have been promising. However, the glue-assisted technique is not without lens related and other complications and the length of follow-up compared to scleral sutured patients is far shorter.[8,13,14]

IOL-related complications are more frequent in eyes with a larger hWTW and a longer axial length.[8] It is noted that haptics will be placed under more stretch in these cases, and that there is shorter externalized haptics to thread into the scleral tunnel. In larger eyes, haptic slippage may occur because of inadequate length of haptic exteriorized through the sclerostomy and from the tension placed on the haptic with subsequent recoil after tunneling. IOL tilt may occur as it is more difficult to orient the haptics in the correct plane in order to avoid tilt when there is less haptic available to thread into the tunnel. Optic capture may be due in part to an anterior shift or vaulting of the optic forward when the haptics are put on stretch when tunneled into the scleral pockets. Many 3 piece IOL's have anterior angularization of the haptics from 5-10 degrees which will be lost when the haptics are put on stretch.

Studies have shown variability in measuring sulcus diameter depending on imaging modality.[9, 15-17] Measuring WTW distance using optical biometry (i.e.IOLMaster™) has been shown to be accurate and reproducible.[18]As some studies have shown a correlation between ciliary sulcus diameter and hWTW,[16] we believe hWTW may be reflective of the distance the haptics need to travel to be externalized through the sclerostomy.[16]There is debate as to whether or not the hWTW is correlated with axial myopia. Some studies have shown that high axial myopia and WTW are inversely proportional,[18]while others suggest that the longer axial length in myopes is associated with an increase in all dimensions of the eye.[19-21] Our study did not show a strong correlation between hWTW and AL, and AL was not significantly predictive of IOL complications. There are several modifications that may be considered in cases of large hWTW. The literature suggests that the horizontal WTW distance is greater than the vertical WTW distance.[22-24]One potential modification is orienting the haptics vertically in patients with large hWTW diameters.[22] In two separate studies, Jacob et al and Narang et al suggested anteriorizing the sclerostomy sites bringing them closer to the limbus, there by shortening the distance the haptics need to stretch and providing more haptic length for tunneling.[25,] Our practice has been using the Sensar AR40e IOL due to its PMMA haptic material and haptic design. We have not noted a decrease in optic capture, haptic deformation, haptic breakage and kinking with Sensar AR40e IOL. In conclusion our technique of scleral fixated IOL had less complications, stable IOL fixation , reduced surgical time, shorter learning curve eyes, good refractive outcome and without suture or glue related complications Large eyes with >12 mm hWTW experienced higher rates of IOL related complication. In these eyes we suggest modification in surgical technique similar to glued IOL. Longer axial length did not contribute to IOL related complications. Future comparative randomized trials are needed to determine the long-term outcome and safety of our technique in comparison with other methods of scleral fixated IOL.

In conclusion, sutureless glueless flapless scleral fixation of IOL is a safe surgical option in eyes without capsular support with fewer complication, stable IOL, reduced surgical time, shorter learning curve, good refractive outcome and without any suture or glue related complications.

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Efficacy of Amniotic Membrane in External Dacryocystorhinostomy

- Dr Vasudendra Nittur[1], Dr Chaitra[1]
[1]MM joshi Eye Institute, Hubli, Karnataka

Abstract

Purpose:

To assess the efficacy of amniotic membrane (AM) transplantation during external dacryocystorhinostomy (DCR).

Study Design:

Prospective comparative interventional case series

Methods:

One hundred consecutive participants underwent external DCR with (n=50, Group 1) or without (n=50, Group 2) AM transplantation. In external DCR with AM, a multilayered AM was placed as a spacer in the osteotomy opening and held in place by suturing to the periosteum lining the margins of the osteotomy as well as to the posterior surface of anterior flaps. All patients had minimum 6 months of follow up. Success rate of surgery was evaluated at the last follow-up after syringing of the nasolacrimal passage.

Results:

Mean age of the patients was 48.64±13.12 years in group 1 and 50.28±14.23 years in group 2. Overall there were more females (64% and 62% in group 1 and 2 respectively). Average duration of surgery was 26.32±4.8 minutes in group1 and 34.28±5.1 minutes in group 2 (p>0.05). Success rate at 6 months was 92% for group 1 and 94% for group 2 (p>0.05). DCR surgery failed in 4 patients (8%) in group 1 and 3 patients (6%) in group 2 (p>0.05).

Conclusions:

Although statistically non- significant, the success rate of DCR was slightly higher with adjuvant AM treatment. Use of amniotic membrane during DCR has the potential to increase the success rate of external DCR.

Key words- DCR, Amniotic membrane

Introduction

Among the diseases of ocular adnexa, infection and blockage of nasolacrimal passage are very common and troublesome conditions. These may be of congenital or acquired etiology. External dacryocystorhinostomy (DCR) is one of the most commonly performed surgical procedures for the management of these cases. Initially described by Toti in 1904 [1] the modern external flap technique was further developed by Dupuy-Dutemps and Baerrget.[2] Since then, DCR has proved to be a reliable operation for obstruction beyond common canalicular opening. Modifications in the surgical steps of original procedure have been introduced over the years for better surgical outcomes without altering its basic concept. Although DCR enjoys a good surgical success rate, failure is still encountered in some cases. Various factors are associated with failed DCR and fibrosis at the ostium site is known to be one of the common causes. Amniotic membrane has been successfully used for its anti-scarring properties in ocular surface disease, and eyelid and socket reconstruction.[3] We hypothesized that use of amniotic membrane to cover the ostium site during DCR surgery would prevent or retard the fibrosis and hence has the potential to increase overall success of the surgery. The aim of the present study was to determine the efficacy and outcomes of use of adjuvant amniotic membrane during external DCR surgery.

Methods

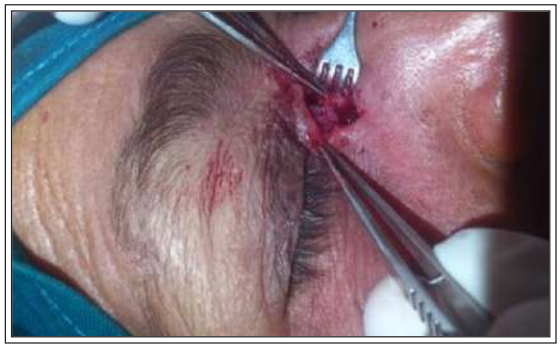
A prospective randomized case control study. The study followed the tenets of the declaration of Helsinki and was approved by the Institutional Review Board of the hospital. One hundred consecutive cases with chronic dacryocystitis with or without mucocele aged between 22 to 80 years were randomized into 2 groups (Group 1: external DCR, Group 2: external DCR with Amniotic membrane). A complete history was obtained in every case and thorough clinical examinations were performed. Preoperatively, irrigation and probing was performed including measurement of tear meniscus height and preoperative irrigation and probing. Cases with external lacrimal fistula and failed DCR were excluded.

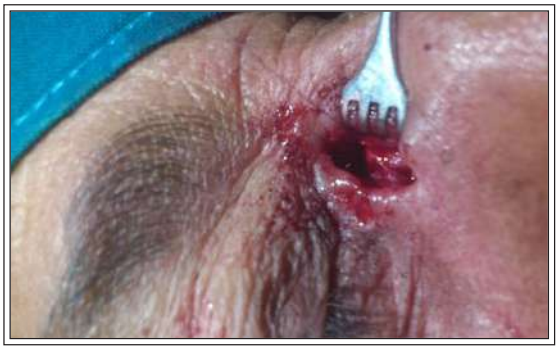
Surgical technique

All surgeries were performed under local infiltration anesthesia. The nasal cavity was decongested for 10 minutes with cotton pledgets soaked in 2% lidocaine with adrenaline (1:200000) and 0.025% xylomethazoline. Initially, a curved 10-11 mm skin incision was placed 3.5 mm nasal to the medial canthus. The orbicularis muscle was bluntly dissected and anterior limb of the medial canthal tendon and periostium were exposed. The skin and the orbicularis muscle were then raised medially as well as laterally with two cats paw forceps. The exposed periostium was incised parallel to the

anterior lacrimal crest and an osteotomy of 12 x 12 mm wide was created with the Citelli's bone punch. With the help of number 11 Bard-Parker blade, first lacrimal sac and then nasal mucosa were opened in an H-shaped fashion forming a large anterior and small posterior flap, and then Bowman's probe was removed. Both the posterior flaps of sac and nasal mucosa were excised. In DCR with AM group a multilayered AM was prepared and placed as a spacer in the osteotomy opening (Figure 1a). Amniotic membrane was held in place by suturing to the periosteum lining the margins of osteotomy (Figure 1b) as well as to the posterior surface of anterior flaps. Subsequently, anterior flaps of the nasal mucosa and lacrimal sac were closed with interrupted 6/0 vicryl sutures. The orbicularis and skin incisions were closed with interrupted sutures and running 6/0 sutures respectively. At the end of the surgery antibiotic drops were instilled in to eye, antibiotic ointment applied to operated site and dressing was done.

Figure 1a-Insertion of amniotic membrane into the osteum; **1b**- suturing of the amniotic membrane





Postoperative treatment consisted of oral cifixime 200 mg twice daily, 0.025% xylomethazoline two drops in each nostril thrice daily and ofloxacin 0.3% eye drop four times daily, for one week. Follow-up examinations were scheduled on 1st week, 1st month, 3rd month and 6th month postoperatively. Epiphora was evaluated with Munk's score (Table1).[4] Criteria for failure of DCR included non-patency on irrigation or tear meniscus height ≥ 2 mm in the postoperative period. Any case with Munk's score >1 in the post operative period was labeled as failed DCR. Intranasal examinations with a nasal endoscope with video attachment were carried out for all the patients at 1 week and six months postoperatively. The operation time (from the incision on the skin to the end of closure of skin incision by suturing) of each case was recorded. Group means were compared using a Student's *t* test and P Value <0.05 was considered significant.

Table 1- Munk's score for epiphora

Grade	
0	No epiphora
1	Occasional epiphora requiring dabbing less than twice a day
2	Epiphora requiring dabbing 2-4 times/day
3	Epiphora requiring dabbing 5-10 times/day
4	Epiphora requiring dabbing >10 times/day
5	Constant tearing

Table 2- Symptoms at the time of presentation in both groups

Symptoms	Group 1		Group 2		Total	
	n.	%	n	%	n	%
Epiphora	18 (36%)	36	16	32	34	34
Epiphora With Discharge	28(56%)	56	26	52	54	54
Swelling in lacrimal sac area	4(8%)	8	8	16	12	12

Results

One hundred DCR surgeries were performed during the study period. The various presenting symptoms in both the groups are shown in table 2.Chronic dacryocystitis was the commonest indication for DCR in both the groups (92% in group 1 and 88% in group 2) followed by mucocele (16% in group 1 and 12% in group 2). Patient characteristics and average surgical time in both the groups are shown in table 3 .On an average there was a mean difference of 7.96 minutes between the two surgical techniques(P=0.12) .The intraoperative complications noted were severe bleeding (6%), injury to the

nasal mucosa (4%) and entry into ethmoidal air cells (2%). Main post operative complication was epistaxis (18% in group 1 and 16% in group 2). There was no difference in the complication rates between the two groups. Objective and subjective success are shown in table 4. Objective success rate at 6 months was 92% for group 1 and 94% for group 2(P=0.21). Subjective success at last follow up was 90% in group 1 and 92% in group 2, which was not statistically significant(P=0.10). Seven patients had failed DCR (4 in group 1 and 3 in group 2). Repeat evaluation of these patients revealed narrowed ostium (n=4) and soft tissue scar (n=2) or membrane across the ostium (n=1).

Table 3- Patient characteristics and average surgical time in both the groups

Characteristics	Group1	Group 2
Number of patients(n=100)	50	50
Age (mean with SD) (years)	48.64 (13.12)	50.28 (14.23)
Age (range) (years)	22–75	24–80
Sex (male/female)	36/64	38/62
Duration of symptoms (mean) (months)	29.8 (range:12–240)	37.4 (range: 12–216)
Laterality of surgery (right/left)	54/46	53/47
Average surgical duration (minutes)	26.32±4.8	34.28±5.1

Table-4 Surgical outcomes at the end of 6 months

	Objective evidence (irrigation and tear meniscus height) Group1: Group2	Subjective evidence epiphora (Munk's scale) Group1: Group2
Success	46:47	45:46
Failure	4:3	5:4
Percentage of success	92:94	90:92

Discussion

External dacryocystorhinostomy has its own limitations with reported failure rate ranging from 0 to18%.[5-9] Several modifications in the surgical technique have been suggested in order to improve the outcome of surgery.[10-13] Meticulous attention to atraumatic handling of the soft tissues, properly placed and uniform rhinostomy with smooth edges, careful dissection to expose the true lumen of the lacrimal sac, followed by careful suturing of mucosal flaps, are important determinants of the outcome of the surgery. Furthermore, individual response to tissue healing process is also an important factor for a successful DCR surgery.[6] Common causes associated with failure of DCR include fibrosis at the site of ostium and inappropriate size and location of the bony ostium. We used AM to cover the ostium during DCR surgery in a bid to reduce the fibrosis and subsequent failure of the surgery. The role of amniotic membrane in various ophthalmic disorders is well-known mainly due to its anti-angiogenic, anti-scarring and anti-inflammatory properties.[3] We found slightly better success rate at the end of 6 months in cases with DCR and AM although this difference was no statistically significant. Overall success of the surgery was measured objectively as well as subjectively in all the patients. Moreover, we found that use of amniotic membrane did not increase the average surgical duration when compared to conventional DCR. More recently, endonasal laser and intracanalicular laser DCR have been gaining in popularity over traditional DCR owing to the advantages of no scar, less tissue damage and less intraoperative time. However, these procedures have their own limitations and long term results are not yet available.[6]

We believe that the modification of DCR with AM is simple yet effective surgical technique that has a potential to increase the overall success rate of conventional DCR surgery. The obvious limitations of the present study include small sample size, lack of proper randomization and short-term follow-up of cases in the postoperative period. We observed slightly lower success rate in external DCR group without amniotic membrane (Group1) compared to previous studies on external DCR that could be because of small sample size. We believe that larger studies with long-term, planned follow-up can further substantiate our results. Furthermore, future comparison of AM with other anti-fibrotic agents such as intraoperative mitomycin and 5-fluorouracil may be of benefit.

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Conflicts of Interest- None

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Pediatric normative Retinal nerve fiber layer (RNFL) thickness in south Indian population

Dr. Rajyashree. S[1], Dr. Nirmal prasad[1]
Department of Ophthalmology, JJM Medical college, Davanagere.

Abstract

Purpose-

To study the retinal nerve fiber layer (RNFL) thickness in pediatric age group and its correlation with age, gender, refractive error and axial length

Methods-

Prospective observational study of 200 eyes of 100 children aged between 5-18 years presenting to the ophthalmic department. All children underwent detailed ophthalmic evaluation and SD OCT examination for RNFL thickness, Standard RNFL assessment protocol was used. Mean RNFL thickness in micrometers along the whole circle circumference, four quadrants, 12'o clock hours were obtained. RNFL measurements included average/full circle thickness – RNFL-FC (360ºmeasure), temporal quadrant thickness, RNFL-T, superior quadrant thickness, RNFL-S, nasal quadrant thickness, RNFL-N, inferior quadrant thickness, RNFL-I.

Results-

Mean age was 13.3±2.4 years.The refractive error in spherical equivalent was -0.28 ± 0.91 dioptre (SE). The mean axial length was 23.1 ± 0.7mm. The mean global RNFL thickness (RNFL-FC) was 97.0±8.8mm (range 79.4 -114.6). RNFL thickness was maximum in the inferior quadrant (RNFL-I) 126±13.7mm followed in order by superior (RNFL-S) 126±16.3mm, nasal (RNFL-N) 70.5±12.3mm and temporal (RNFL-T) 63.4±9.2mm, in both the sexes. For every increase in one diopter of spherical equivalent of refractive error the mean RNFL increased by 3.77 microns and there was a reduction in mean RNFL thickness by 4.86 micron for every 1mm increase in axial length.

Conclusion-

RNFL varied minimally with gender. Positive correlation was seen with refractive error while inverse or negative correlation was seen with axial length and age. RNFL measurements could serve as reference for further studies on pediatric glaucoma or other optic nerve head pathologies.

Key words- RNFL thickness, Paediatric age group, Optical coherence tomography

Introduction

The diagnosis and follow-up of children with an ocular disease is more difficult than that of adults because of the challenge in obtaining reliable and reproducible visual examinations. Important diagnostic tools used in adults, such as visual fields, require their cooperation. For children, such tools are often impractical because the results are unreliable, and hence difficult to interpret However, OCT provides objective measurements of the affected structures. Generally, children older than 3 or 4 years of age can cooperate sufficiently. Macular measurements are even easier to obtain than those of the optic nerve, making OCT particularly suitable for use with uncooperative children or those with poor fixation. The potential value of OCT in diagnosis of childhood glaucoma has also been demonstrated recently.[1] OCT provide objective information of optic disc configuration and/or RNFL thickness and may represent valuable tools in the evaluation of children with subnormal vision and in children with known diseases that may affect the optic nerve, such as craniopharyngioma and glioma. In children with binocular subnormal vision, a normal database is necessary for purposes of comparison. Similarly, in order to assess children with monocular subnormal vision, we need to know the normal range of differences between the two eyes. Normal databases have been established for both HRT and OCT, but these have been determined in adults and may not be applicable to children.[2] Hence we did this study to assess the normal RNFL thickness in south Indian pediatric normal.

Material and Methods

Prospective observational OCT based study of 200 eyes of 100 children who presented to the ophthalmic outpatient department from November 2019 to August 2020.The study was approved by the Institutional review board. Any child aged 5 years to 18 years but cooperative for OCT with no asymmetry in cup-disc ratio and without optic nerve head abnormalities were include in the study. Children with strabismus

or amblyopia, abnormalities of the disc or the retinal nerve fiber layer, Family history of glaucoma, any other hereditary eye disease, history of intraocular surgery or any kind of laser therapy, Mentally challenged children with neurological, metabolic or vascular disorders, systemic disease possibly affecting the eye, Ocular media opacity, Best-corrected visual acuity of less than 20/30, hypermetropia more than +5D and myopia more than –5D or astigmatism ≥ 2D were exclude from the study.A detailed history including demographics, information on past medical illness and drug intake and their duration was recorded .Ocular diseases if any was noted. The complete Ophthalmological examination was done in all children. Vision was assessed carefully using Snellen's chart. Pupil was also tested for any afferent pupillary defect, which grossly tests optic nerve function and retinal functions .cycloplegic refraction was done in relevant cases. A thorough examination of the eyes was carried out under slit lamp. Fundus evaluation was done using Direct and Indirect ophthalmoscope with special attention to any opacity in the lens, vitreous hemorrhage and retinal detachment.

Spectral-domain OCT was performed with the Cirrus HD-OCT-500. This has an acquisition rate of 27,000 A-scans per second. The protocol used for RNFL assessment was the optic disc cube where a 3.46 mm circular scan is placed around the optic disc and the information about parapapillary RNFL thickness is obtained where by 27,000 A scans are acquired per second. All images were reviewed and only images with good signal strength with no movement artifact were included for the study. The parapapillary RNFL thickness parameters automatically calculated by the Cirrus software and evaluated in this study included average/full circle thickness – RNFL-FC (360ºmeasure), temporal quadrant thickness, RNFL-T , superior quadrant thickness, RNFL-S , nasal quadrant thickness, RNFL-N , inferior quadrant thickness, RNFL-I. Three such circular scans were performed successively. The average of the 3 scans was used in the analysis. All scans were performed by the same investigator. Mean RNFL thickness in micrometers along the whole circle circumference, four quadrants, 12'o clock hours were obtained. Both eyes of every subject were selected for statistical analysis. Data were entered in a excel sheet, and then transferred to the statistical package for social science program for data management and analyses. Results were expressed as mean±SD, range and normal value (95% confidence intervals) calculated according to age, gender and laterality of eyes. Unpaired t-test was used to compare between two groups (male v/s female, right eye v/s left eye). Correlation and regression analysis was done to assess the relationship between RNFL and clinical parameters (age, sex and refractive error).A P-value 0.05 or less was considered for statistical significance. SPSS (version 16) software was used for all the analysis.

Results

The age of the patients in this study ranged from 5 to 18 years with the mean of 13.3±2.4SD.There were 14 children in age group between 6-10 years, 56 children in age between 11-14years and 30 in the age group between 15-18 years. The study had 65 males and 35 females. The unaided visual acuity of all the eyes ranged from 6/6(log MAR 0.0) to 6/36(log MAR 0.778) with mean refractive error of -0.28 ± 0.91 diopters (range-4 to +2.5) .The axial length varied from 21.7 mm to 25.7mm with the mean of 23.0±0.7 SD. The difference of mean axial length and the refractive error was not statistically significant between the right and the left eyes. Mean Global RNFL thickness and distribution of RNFL in each quadrant shown in Table 1. The mean global RNFL thickness(RNFL-FC) was 97.0±8.8mm(range 79.4 -114.6).The RNFL thickness was maximum in the inferior quadrant (RNFL-I) 126±13.7mm followed in order by superior(RNFL-S)126±16.3mm ,nasal (RNFL-N) 70.5±12.3mm and temporal(RNFL-T)63.4±9.2mm ,in both the sexes. Seventy six children had global RNFL (RNFL FC) thickness ranging from 86.0-105.9 μ.When comparing the mean RNFL between both sexes females had thicker RNFL than males(Table2) which was not statistically significant (p<0.37).However when the nasal quadrant (RNFL-N) between both sexes was compared the mean difference was 4.40 with P value<0.03.The inter-ocular variations in RNFL thickness in normal children measured by SD OCT .The mean global RNFL thickness was 97.7±9.2SD in right eye (range 74.4-116mm) and 96.3±8.4SD in left eye(range 79.5-113.1) .The mean difference in global RNFL thickness between the two eyes was 1.38 with P value <0.27 which showed no statistical significance.

Mean global RNFL thickness and thickness of RNFL in each quadrant according to the age groups shows as age increases the mean RNFL thickness as well the thickness in each quadrant decreases (Table 3 and Figure 1). The RNFL thinning was found to be more in the surerior quadrant(RNFL-S) .In order to assess the relationship between the age and the RNFL thickness correlation analysis was done .The analysis revealed that there is negative correlation between age and RNFL which shows that there is decrease in RNFL with increasing age(r=0.19) .Though this relationship was weak, regression analysis was carried out to know the RNFL reduction for every 1yr increase in age. Analysis revealed that there was reduction of 0.70 micron in RNFL for average increase of one year. Explained variation was found to be (3.6%) R^2=0.036(P=0.008).

Table1-Mean Global RNFL thickness and distribution of RNFL in Each quadrant

Variable	Total	
	Mean±SD (micron)	Normal Range (micron)
RNFL-FC	97.0±8.8	79.4-114.6
RNFL-S	126.2±13.7	98.7-153.7
RNFL-I	127.7±16.3	95.2-160.2
RNFL-N	70.5±12.3	46.0-95.0
RNFL-T	63.4±9.2	45.0-81.9

Table 2-Variation in the RNFL thickness between Male and Female in normal children

Variable	Males		Females		Males v/s Females		
	Mean ± SD	Normal Range(micron)	Mean ± SD	Normal Range	Mean Diff	t value	P value
RNFL-FC	96.6±8.9 (micron)	78.7-114.4	97.8±8.6	80.6-114.9	1.19	0.91	0.37,ns
RNFL-S	126.7±13.5	99.6-153.7	125.3±14.2	96.9-153.7	1.36	0.65	0.52,ns
RNFL-I	126.7±16.7	93.4-160.1	129.6±15.4	98.9-160.3	2.85	1.20	0.23,ns
RNFL-N	69.0±10.7	47.2-90.7	73.4±14.1	45.1-101.7	4.40	2.24	0.03*
RNFL-T	63.9+9.7	44.5-83.4	62.5±8.2	46.1-78.9	1.44	1.10	0.27,ns

Table 3-RNFL thickness with age

Variable	6 - 10 Yrs (n = 29)		11 - 14 Yrs (n = 110))		15 - 18 Yrs (n = 61)	
	Mean ±SD	Normal Range	Mean ±SD	Normal Range	Mean ±SD	Normal Range
RNFL-FC	100.2±6.4	87.5-112.9	96.6±8.9	78.9-114.4	96.2±9.4	77.4-115.0
RNFL-S	133.4±15.7	102.0-164.8	124.8±11.6	101.7-147.9	125.5±15.7	94.1-156.8
RNFL-I	130.4±14.9	100.6-10.1	127.0±17.5	92.0-162.0	127.9±14.5	99.0-156.9
RNFL-N	70.6±8.4	53.7-87.4	70.5±12.6	45.4-95.6	70.6±13.3	44.0-97.1
RNFL-T	65.8±7.3	51.1-80.5	64.3±9.8	44.7-83.8	60.8±8.5	43.8-77.8

Figure 1- Relationship between Age and RNFL Thickness

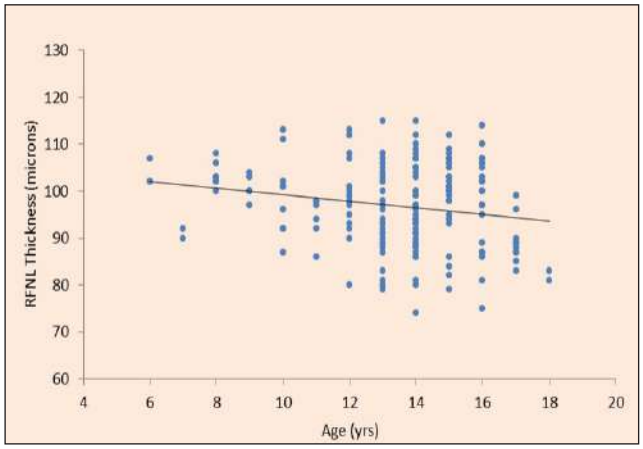


Figure 2-Relationship between R efractive error and RNFL Thickness

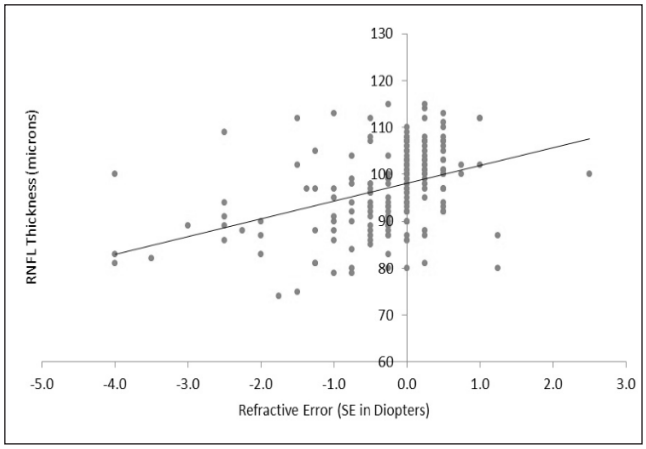
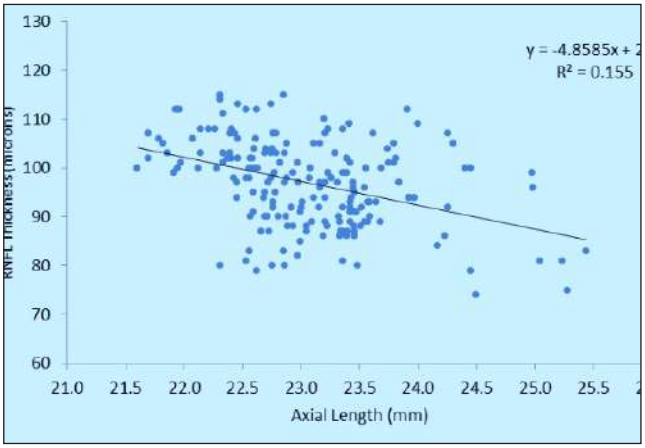


Figure 3- Relationship between Axial Length and RNFL Thickness



Significant positive correlation coefficient of 0.38 with refraction error in spherical equivalent(SE) with regression coefficient of 3.77(Figure 2).On analysis it was found that for every increase in one diopter of spherical equivalent the mean RNFL increased by 3.77 microns Explained variation was found to be 15.2%(R^2=0.036)(P < 0.001).Correlation and regression analysis between axial length and RNFL thickness revealed negative correlation between axial length and RNFL thickness(Figure 3), which shows there is reduction in mean RNFL thickness by 4.86 micron for every 1 mm increase in axial length. The explained variation was found to be 15.2 % (R^2=0.155)(P < 0.001).The correlation and regression analysis between RNFL thickness with respect to age, refractive error and axial length are shown in Table 4. Positive correlation was seen with refractive error while inverse or negative correlation was seen with axial length and age.

Table 4- Correlation & Regression Analysis between RNFL thickness and age, refractive error and axial length

Relationship between	Corr.Coeff 'r'	Regn.Coeff 'ß'	Relation Equation	R^2
Age & RNFL	-0.19	-0.70	RNFL = 106 - 0.70 Age	0.036 (3.6%)
Ref.Error & RNFL	0.38	3.77	RNFL = 98 +3.78 RefEr	0.152 (15.2%)
AXL & RNFL	-0.39	-4.86	RNFL = 209 - 4.86 Axl	0.155 (15.5%)

R^2 = Explained variation

Discussion

OCT has become widely used tool in clinical and scientific ophthalmology .Its uses in diagnosis of diseases is not restricted only to ophthalmology. Beside its use in identifying macular pathology and glaucoma, in recent year its application to diagnose various ocular conditions has widely been expanded such as multiple sclerosis, optic nerve gliomas, peudotumor cerebri, optic neuritis and papilloedema.[3-6]

Normative data are provided automatically by OCT but the data base only include individuals 18years and above limiting its use in children .The application of OCT in children has been documented in several studies.[7-10] However minimal literature on normative data base exist which would serve as a bench mark for reference and glaucoma scanning.[11] The average RNFL thickness in our study was 97.0± 8.8µm .When compared to other studies in the past, the average RNFL of our study was lower to those studies done previously. In a large study conducted by Huynh et al[12] the average RNFL thickness was 103.7±11.4µm.The average RNFL in our study was lower to those of salchow et al[13], Qian et al[14], EL-dairi et al[7], Leung et al[15], and Ahn et al[16].Bourne et al[17] compared the OCT 2000 with the Stratus OCT and found that the former model consistently yielded a higher RNFL thickness value .In comparison the study conducted by Elai et al[18], Barrio-Barrio et al[19], Al-Haddad et al[20] using cirrus OCT yielded results that were consistent with our finding. The RNFL thickness varies significantly among types of OCT used and therefore direct comparison of RNFL thickness measurement among OCT instrument like Stratus and Cirrus may be misleading.[11] The distribution of RNFL thickness (thickest inferiorly and superiorly and thinner nasally and temporally)are in agreement with the normal distribution of RNFL. These variation are the result of the large number of nerve fibres converging to the optic nerve head from the superior and inferior arcuate bundles, relative to the number of fibres converging from the papillomacular bundles and nasal retina. Studies vary as to whether the RNFL was thicker temporally or nasally or whether it was thicker superiorly or inferiorly. In our study it was seen that, in the age group between 5-10 years, superior RNFL was thicker compare to the inferior RNFL, with increasing age more thinning was seen in the superior RNFL compare to inferior RNFL, thinning was also seen in temporal RNFL while minimal changes were detected in the nasal RNFL.[12]

Large number of studies has shown that RNFL thickness decreases as age increases.[21,22,23] It has been confirmed by several studies that the number of ganglion cells in human retina decreases with age which results in thinning of the RNFL .This has been confirmed by several investigation using OCT.[24-25] It has been estimated that normal individual lose ganglion cells at a rate of 4909 per year.[26]Bundez et al[23] found that RNFL was thinner in older people with decline of appoximately 2 microns per decade. Qian et al[14] and salchow et al[13] reported that

RNFL thickness tends to increase with age in a population younger than 18 years. B Alamouti et al[25] studied 100 individual to establish changes in RNFL thickness with age in their study .They found highly significant correlation of both the retinal and the RNFL thickness with age. In these study the retinal thickness decreased by 0.53 µm per year. About 80% of the changes in retinal thickness over time are caused by shrinkage of the RNFL. Poinooswamy *et al*[27] examined 150 healthy volunteers of different ages using scanning laser polarimetry. They found a progressive reduction of the RNFL thickness with increasing age. The data presented in their study indicate a significant reduction of the RNFL thickness of 0.38 µm/year. In this present study we analyzed that there was mean global decrease in the RNFL, as well as decrease in RNFL in each quadrant with increasing age. The decrease in RNFL was more in superior quadrant compare to inferior quadrant, thinning was also seen in temporal quadrant while it was absent in nasal quadrant .Age was correlated negatively with RNFL thickness. In study conducted by Rajul S Parikh[28], it was seen that RNFL tends to decrease with age .Average RNFL and RNFL by quadrant decreases especially after 50 years of age .Thinning of the RNFL is not uniform in all with maximum loss in the superior quadrant in comparison to inferior quadrant which is more resistant to loss. These findings were consistent in our studies also.

The effect of refractive error has been widely debated .Many studies have demonstrated positive correlation with spherical equivalent.[12,13,14,29] Huynh et al[10] studies on 1765 children less than 6 years reported significant trend for thicker RNFL with more positive refraction, however the changes were small. Qian et al[14] reported a positive correlation of the average RNFL thickness with refractive error in healthy children. Merugacz et at[1] compared RNFL thickness between 30 myopic and 15 controlled participants without myopia and reported no significant difference between the two groups. Vernon et al[30] conducted similar study on 31 highly myopic eye of caucasian origin and observed no statistically significant correlation between the RNFL and spherical equivalent. A.Rao et al[11] found that axial length and refractive status accounted for only 10% of the variation in RNFL thickness. In our study significant correlation was established between refractive error and global RNFL thickness, which showed regression coefficient to be 3.77. There was increase in mean RNFL thickness by 3.77 microns for every unit diopter increase in refractive error. The relationship between RNFL with axial length has been established in many studies. Sony et al[31] and Bayratkar et al[32] reported no significant correlation between the RNFL average thickness and axial length, however these studies were limited by small sample size .While Huynh et al[10] found significant trend toward thinner RNFL with longer axial length. Knight et al[21] observed that axial length had a negative correlation with the mean RNFL thickness but had a positive correlation with the temporal quadrant in 63 chinese children. Cheung et al[33] reported that longer axial length was associated with thinner RNFL in a population based study of Chinese adults. A. Rao et al[11] in their study reported that the longer the axial length and greater the myopic shift early in life, the thinner will be the RNFL thickness. In our study negative or inverse correlation is seen (R^2=0.155) with regression coefficient of -4.88 which shows that for every 1 mm increase in axial length, RNFL l decreases by 4.88 microns.

The retinal nerve fiber followed a normal distribution. RNFL varied minimally with gender, RNFL thinning was associated with increasing axial length and less positive refraction. The normative data from this study could serve as reference for further studies on pediatric glaucoma or other optic nerve head pathologies using nerve imaging modalities.

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Pressure Induced Interlamellar Stromal Keratitis (PISK)

- Dr. Dr. Krishnaprasad Kudlu MS[1]
[1]Prasad Netralaya, Udupi, Karnataka

Etiology -

In the setting of LASIK/SMILE, PISK is a relatively rapid steroid response resulting in high intraocular pressure with resulting fluid accumulation in the interface. The amount of fluid present may be relatively small, resulting in diffuse haziness in the interface and overlying stroma without an obvious fluid layer[1] [Figure1], or it may be pronounced [Figure 2], resulting in a visible fluid cleft separating the anterior flap from the posterior residual bed.[2] PISK appears to be a more complex entity to identify than other interface complications due to confusing nomenclature in the literature and to the wide variety of appearances and findings on presentation.

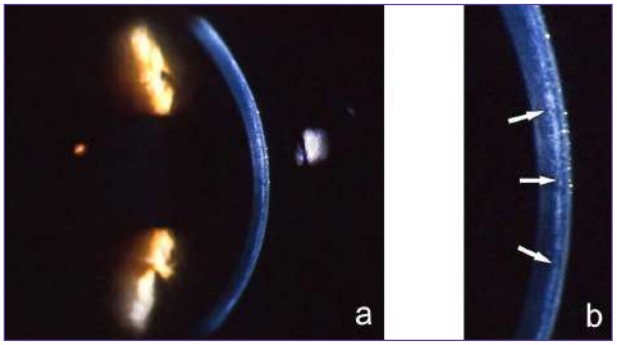

Figure 1-PISK with diffuse, hazy interface but without an obvious fluid layer

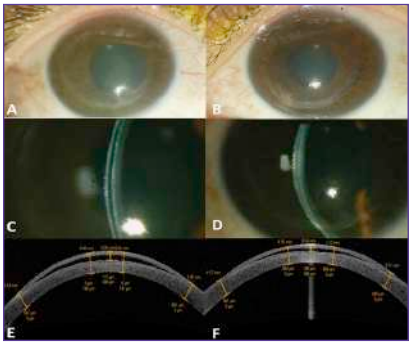

Figure 2- PISK with an obvious fluid cleft

Multiple names have been given to the various manifestations of this entity, potentially resulting in confusion and misleading diagnostic criteria. Among the most common terms are pressure-induced stromal *keratitis* (PISK),[1] pressure-induced interface *keratitis*,[3] and interface fluid syndrome (IFS).[4,5] "Keratitis" is a misnomer in this condition, as confocal evaluations have demonstrated that no actual keratocyte inflammation is present.[5,6] Interface fluid syndrome (IFS) is technically correct; however, IFS may occur from a variety of different mechanisms unrelated to acute steroid response in the early postoperative period, and to many clinicians the term implies that interface fluid that is readily visible. Therefore, while correct, we recommend against the routine use of IFS to communicate information about this specific entity occurring in the early postoperative period after LASIK associated with steroid use and presenting with or without obvious interface fluid. Recently, Tourtas and Cursiefen[7] coined the term "pressure induced stromal *keratopathy* (PISK)," which maintains the most common abbreviated term "PISK" while also accurately and most effectively communicating the etiology of the condition. We therefore recommend this term be adopted moving forward and will use it throughout this review.

Management- While PISK has been described in detail,[1-6, 9-11] the significant variability in clinical presentation, from diffuse haze to demonstrable interface fluid, requires added diligence in establishing the diagnosis, differentiating this condition from diffuse lamellar keratitis (DLK), and initiating an appropriate treatment strategy. The degree of interface fluid accumulation masks true IOP in various ways when measured using standard approaches. In all cases, actual IOP is greater than IOP measured centrally, and peripheral measurements generate a more accurate IOP. With small amounts of fluid, IOP measurements may be elevated but still falsely low, while with larger fluid clefts IOP will measure extremely low due to the cushioning effect of the interface fluid. For any patient on chronic steroids after LASIK (two weeks or longer), it is critical to routinely measure IOP, even in the early postoperative period. IOP measurement, especially when obtained centrally, is artifactually reduced in a predictable way after routine LASIK[12]; therefore, any increased IOP postoperatively warrants further investigation. Whenever IOP measurements are suspect, alternative means should be attempted to determine IOP, including peripheral IOP measurements with Goldmann applanation or tonopen.[13-16] Dynamic contour tonometry may also be employed to assess true IOP, as it has been

shown to be relatively immune to changes in corneal biomechanics and pachymetry after LASIK.[16] Appropriate management includes cessation of steroid use and initiating topical anti-glaucoma medications until the fluid resolves.[1-4, 8-10]

Outcome in PISK -Severe glaucomatous field loss and decreased central visual acuity can occur if PSIK is not recognized early and managed appropriately.[2, 3, 8, 9] If identified and appropriately managed early, typically patients do well without loss of BCVA.[1, 11]

A unique case of PISK after SMILE-A rare complication

Abstract

Purpose: To report a case of pressure-induced interlamellar stromal keratitis (PISK) after small-incision lenticule extraction (SMILE) for the correction of myopic astigmatism in the United States. **Methods**: We report the case of a 27-year-old man who underwent uneventful SMILE surgery and presented with pressure-induced stromal keratitis. Anterior and posterior segment examination, uncorrected distance visual acuity, refraction, intraocular pressure, and pachymetry values are reported from this time period. **Results**: Three weeks postoperatively, examination revealed newonset central corneal haze and edema in both eyes, more significant in the right eye. The patient was given a presumptive diagnosis of diffuse lamellar keratitis. Intensive corticosteroid treatment was administered, causing a significant decline in uncorrected distance visual acuity OD from 20/25 to 20/250 and OS from 20/20 to 20/ 60, with a significant myopic shift of 23.0 D and 21.0 D, respectively. In our case, pachymetry measurements revealed 78 mm OD and 43 mm OS of additional corneal thickness. Pressure readings were 25 mm Hg OD and 19 mm Hg OS, respectively. He was diagnosed with PISK, and after 4 days of steroid discontinuation and Brimonidine-Timolol administration, his symptoms had improved with resolution of corneal edema. **Conclusions**: Clinicians should be aware that PISK is a potential complication of SMILE. Postoperative intraocular pressure measurements are an important aspect of the management of postcorneal refractive surgery patients because the differentiation of PISK from diffuse lamellar keratitis, as well as the early detection and treatment of PISK, can avoid severe complications

Key Words: pressure-induced interlamellar stromal keratitis, steroid-induced ocular hypertension, diffuse lamellar keratitis, interface fluid syndrome, small-incision lenticule extraction

Pressure-induced interlamellar stromal keratitis (PISK) has been documented as a rare post-LASIK complication. Patients will present at least 1 week postoperatively with diffuse haze in the corneal interface that is nonresponsive to, or may worsen, with topical steroid treatment.[17] There are previously published reports of PISK after small-incision lenticule extraction (SMILE) to correct myopia or myopic astigmatism during which the femtosecond laser creates a lenticule in the corneal stroma that is removed by the surgeon through a 2 to 5 mm incision, therefore avoiding flap-related complications.[18,19] we report a rare case of PISK after SMILE

Case report

A 27-year-old male patient presented for preoperative evaluation for bilateral SMILE for the correction of myopic astigmatism. His medical history and medications were noncontributory. Preoperative best corrected distance visual acuity was 6/6 in both eyes with a refraction of -5.50DS with -0.50DC at 100 in the right eye and -4.5DS with -1.0DC at135 in the left eye. Slit-lamp and dilated fundus examinations were unremarkable, with no signs of dryness or superficial punctate keratopathy. Intraocular pressure (IOP) was 16 mm Hg RE and 17 mm Hg LE. Central corneal thickness (CCT) was 650 mm RE and 642 mm LE. Specular microscopy revealed endothelial cell density of 2667 cells/mm2 RE and 2500 cells/mm2 LE with a uniform endothelial cell pattern without any sign of guttata or abnormalities. An uneventful SMILE procedure was performed. His postoperative regimen consisted of topical ofloxacin 0.3% 4 times daily and artificial tears hourly BE, as well as topical prednisolone acetate 1% OD 4 times daily for the first week with the daily dose reduced by one drop every week. At his day 1 and week 1 postoperative visits, his uncorrected distance visual acuity (UDVA) was 6/6p RE and 6/6 LE. Manifest refraction at 1 week was +0.5DS with -1.0DC at 73 RE and Plano LE. At this point, IOP was not checked. He was told to continue tapering his medication regimen and return for a 1- month follow-up. However, 1 week later, he presented with suddenly worsening symptoms of hazy vision and foreign body sensation, which started 2 days before the visit. UDVA was 6/18 RE and 6/6p LE. Examination revealed a 1.3-mm abrasion of the central cornea RE with no infiltrates. He was advised to continue ofloxacin along with prednisolone acetate eye drops BE, and a bandage contact lens (BCL) was placed RE. Two days later, the epithelial defect healed and the BCL was removed; however, examination revealed new onset haze in the central cornea RE. Because of suspicion for diffuse lamellar keratitis (DLK), he was prescribed prednisolone acetate eye drops RE every hour while awake for 2 days and then every 2 hours while awake until his follow-up appointment in 1 week and told to continue his scheduled corticosteroid regimen LE. One week later, now 1 month postoperatively, he presented with worsening symptoms of cloudy vision OD, mild soreness BE, headaches, and nausea. He was taking ibuprofen as needed for pain relief and prednisolone acetate as prescribed. His UDVA declined to 6/60 RE and 6/12p LE, and manifest sphere was - 3.00 RE and -1.00 LE. Slit-lamp examination revealed central corneal haze BE and worse RE. Pachymetry readings showed CCT 620 mm RE and 581 mm LE (Fig. 1), which was higher than the expected corneal thickness. Optical coherence tomography (OCT) imaging

(OPMI Lumera 700 with Rescan 700; Carl Zeiss Meditec, Inc, Dublin, CA) showed increased corneal thickness BE, with pockets of interface fluid RE (Fig. 2). IOPs measured at the center of the cornea were 25 mm Hg RE and 19 mm Hg LE. A diagnosis of PISK was made BE. Prednisolone acetate drops were discontinued, and Combigan (brimonidine tartrate/timolol maleate) eye drops was prescribed BID. One week later, the patient had subjective improvement in visual acuity, and his nausea, headache, and pain had fully resolved. UDVA was 6/6 RE and 6/6P LE. Examination revealed a significant improvement in haze OU. OCT showed resolution of the stromal fluid RE and substantial improvement in corneal edema BE. CCT was 554 mm BE. His pressures had resolved to 10 mm Hg RE and 9 mm Hg LE, measured centrally. He was advised to continue therapy with Combigan BID and frequent artificial tears.

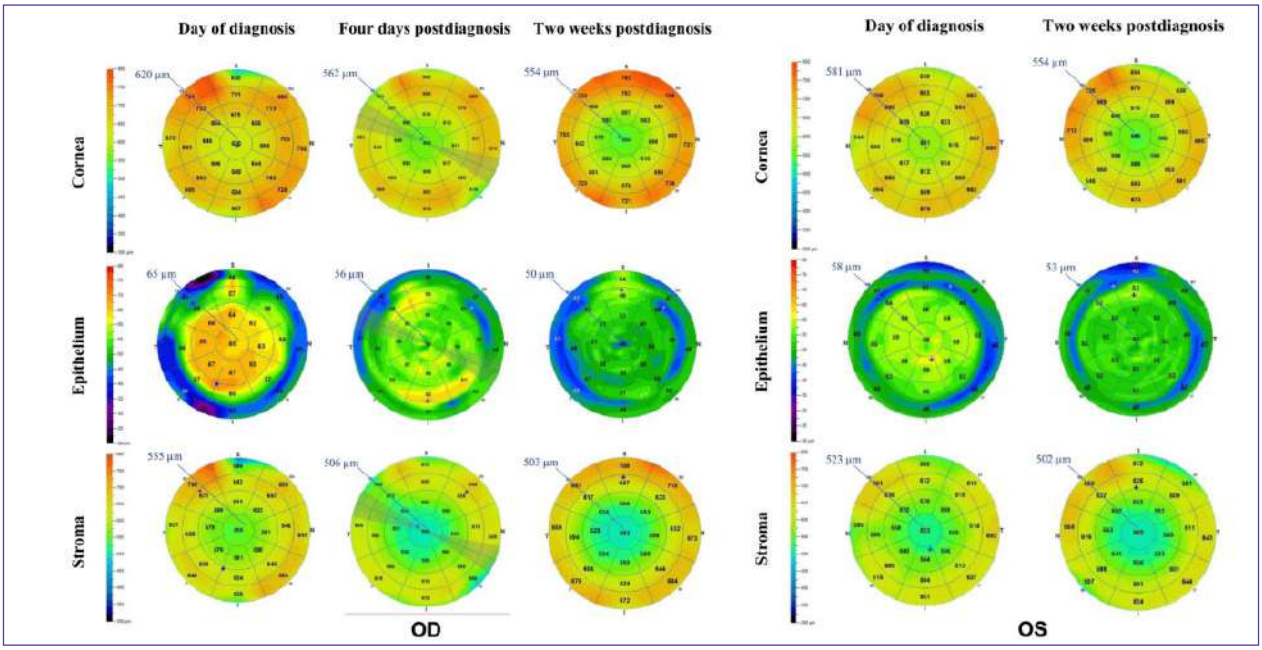

Figure 1. OCT pachymetry RE and LE showing CCT, epithelial thickness, and stromal thickness on the day of PISK diagnosis and after treatment

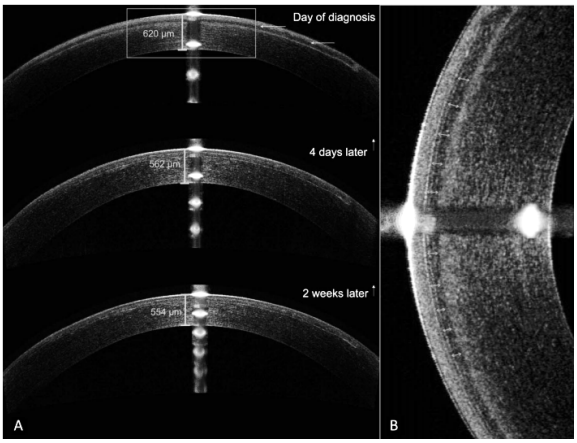

FIGURE 2. A, OCT of the cornea RE showing CCT (green line markers) on the day of PISK diagnosis and posttreatment. Thickness was measured in the optical axis along the superior-to-inferior meridian for consistency. B, Enlarged OCT image of the interface fluid accumulation on the day of PISK diagnosis.

Discussion

PISK is caused by elevated IOP or, more rarely, corneal endothelial cell dysfunction. PISK has been documented after LASIK in several case reports. We report a case of PISK after SMILE surgery. PISK occurs when elevated IOP disrupts the endothelial pump function, which normally acts through active transport to move fluid out of the stroma and maintain corneal deturgescence. The fluid shifts across the endothelium from areas of high to low pressure, and without the endothelial pump function, the corneal cells imbibe the fluid and edema occurs.[20] Normally, this fluid would be seen as microcystic edema in the basal epithelium. However, LASIK and SMILE procedures create a potential low-pressure space in between the corneal flap/cap and stromal bed in which fluid can accumulate, leading to PISK. Our patient had myopia and darkly pigmented irides; perhaps these characteristics placed him at higher risk for developing ocular hypertension and PISK.[21–23] PISK has been historically associated with LASIK, and its incidence is rare. SMILE, however, is a relatively

new procedure. There is only 1 previously reported case of PISK after SMILE, when a patient presented 24 days postoperatively with high IOPs and corneal haze and edema. Within 8 hours of discontinuation of steroids and administration of a topical beta-blocker, topical nonsteroidal antiinflammatory drug, and potent systemic diuretics, his IOP normalized and interface fluid accumulation resolved.

PISK should be differentiated from DLK because their clinical pictures are similar. DLK, or "sands of Sahara," is idiopathic interface inflammation typically occurring within the first postoperative week, and its clinical features range from asymptomatic stromal infiltrate to stromal necrosis. DLK is a well-documented complication of LASIK, and it has also been reported after SMILE.[17,24] It is usually self-limited and responds to topical steroids.[17,25] The exact cause is unknown, but it is associated with epithelial defects at the time of surgery, bacterial endotoxins, red blood cells, meibomian gland secretions, and traumatic flap dislocation.[17,25] PISK can present with a DLK-like interface haze, as observed in our patient in the second postoperative week. As with our patient, pain and worsening visual acuity may occur. Confocal microscopy will show the absence of inflammatory cells, unlike in DLK.[1] PISK typically occurs beyond the immediate postoperative period, sometimes as late as several months after the procedure, and has been documented in postoperative patients with trauma, recurrent erosions, and epithelial abrasions.[17,25] In this case, our patient indeed developed a small central epithelial abrasion, identified 2 weeks after surgery, which was treated with a BCL and preceded increased steroid treatment. We presume that our patient's increased IOP caused disruption of endothelial pumps, and the resulting subclinical microcystic edema led to the breakdown of epithelium and a subsequent abrasion.

Diagnosis of PISK is made by elevated IOP measurement and anterior segment OCT. Many refractive surgeons do not measure IOP on the first day after corneal refractive surgery because of the concern of causing further insult to corneal epithelium. However, IOP should be measured at subsequent postoperative visits, especially when there is suspicion of DLK. In our case, we unfortunately did not measure IOP until 1 month postoperatively. Falsely, low IOP may occur from readings taken over the interface fluid; therefore, IOP should be measured in the corneal periphery.[25] IOP was checked at the central cornea in our patient, and it was likely higher than what was reflected by our measurement. Anterior segment OCT may show pockets of interface fluid, and we recommend performing OCT whenever a SMILE or LASIK patient presents with unexplainable vision loss or if there is an increase in IOP compared with the previous visit. In addition, our patient's pachymetry measurements revealed 78 mm RE and 43 mm LE of additional corneal thickness, representing corneal edema that significantly decreased after the initiation of proper treatment. As expected, this edema was predominantly in the stroma, which decreased by 52 mm RE and 21 mm LE over the next 2 weeks (Fig. 1).Early diagnosis of PISK can reduce the chance of visual field defects or decreased visual acuity from severe glaucomatous optic neuropathy.[25] Treatment is cessation of steroids and initiation of IOP-lowering medications. We recommend topical beta-blockers and, for very high IOPs, perhaps IV mannitol or oral diuretics. Certain antiglaucoma medications such as dorzolamide, which function through inhibition of carbonic anhydrase, disrupt the function of the endothelial pump and can, in theory, exacerbate PISK.[26] Postoperative IOP measurements are important in the management of postcorneal refractive surgery patients because early detection and treatment of PISK can avoid severe complications.

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Acute Macular Neuroretinopathy (AMN) & Para Central Middle Maculopathy (PAMM) in COVID-19

- Dr. Deepika Makam, Dr. Mishra Divyansh Kailashchandra
Dr. Minija CK Dr. Mahesh P Shanmugam
Dr. Nidhi Dubey Dr. Shwetha Suryakanth

Abstract

This is a case report of two patients who primarily presented to ophthalmologist with decreased vision and minimal fundus changes with features of Acute Macular Neuroretinopathy(AMN) and Para Central Middle Maculopathy (PAMM) on OCT(Optical coherence Tomography).Patient with AMN was further identified with COVID19 infection and patient of PAMM with history of COVID revealed a secondary Rhinocerebral and orbital bacterial infection. This case report highlights the importance of OCT in identifying such subtle lesions in patients with bare fundus findings

Keywords: COVID-19 associated maculopathy, Acute Macular Neuroretinopathy(AMN) , Paracentral Acute Middle Maculopathy (PAMM) , Retinal manifestations ,ocular manifestations.

Introduction:

COVID-19 infection was primarily identified with severe acute respiratory syndrome. Over time multi organ involvement with various systemic manifestations have been reported. Various retinal manifestations are also reported.[1]Most of the posterior segment manifestations are believed to be due to inflammatory, vascular and cytopathological changes triggered by viral infection,and not specific to COVID19.[2] These changes induce generalized endothelitis causing microvascular dysfunction and tissue ischemia.[3]Herein, we report 2 cases,one with no history of COVID and second with history of COVID ,but presented primarily with vision complaints,minimal fundus changes,where AMN and PAMM was recognized with OCT.

CASE 1:

A 60-year-old healthy male presented with redness in both eyes (BE) since 1day.He had history of febrile illness with gastrointestinal symptoms 2 days back and was vaccinated with first dose of vaccination(COVAXIN®) for COVID-19 3weeks back. On examination,best corrected visual acuity(BCVA) was 20/20,N6 in BE. Fundus examination of right eye (RE) revealed a single cotton wool spot along superior vascular arcade and left eye (LE) had multiple cotton wool spots along inferior arcade(Fig 1A,2A).On Optical Coherence Tomography(OCT),using Topcon Swept Source DRI OCT Triton

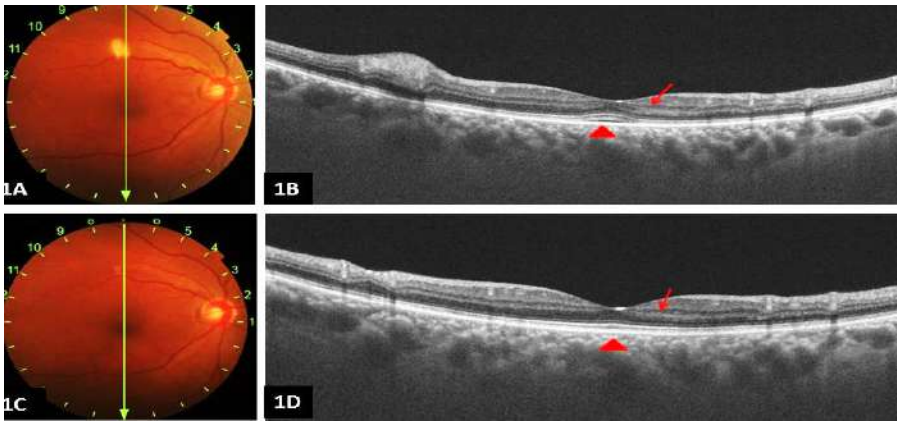

Figure 1 : 1A)Colour fundus photograph showing cotton wool spot
1B)SS-OCT showing hyperreflective thickened outer plexiform layer (arrow) with streak of shallow subretinal fluid(arrow head) .At 6 weeks follow up
1C)Colour fundus photography showing resolving cotton wool spot.
1D) SS-OCT showing normal outer plexiform layer (arrow) and resolved sub retinal fluid (arrow head).

PlusTM shallow neurosensory detachment with focal area of hyper reflectivity in outer plexiform layers(OPL) with focal disruption of ellipsoid zone(EZ) and interdigitation zone(IZ) suggestive of AMN(Fig 1A,1B,2A,2B) . He was advised RT-PCR and antibody titers for COVID-19 to rule out vaccine related immune mediated inflammation. RT-PCR was positive with normal antibody levels. Hence patient was diagnosed to have AMN secondary to COVID-19 infection. Patient was admitted at COVID care center and all investigations, CRP/D-Dimer levels were normal hence he was discharged after quarantine. At 6 weeks,BCVA was20/20 N6 in both eyes, fundus showed resolving cotton wool spots and OCT showed resolved neurosensory detachment, normal appearing OPL,EZ and IZ(Fig 1C,1D,2C,2D)

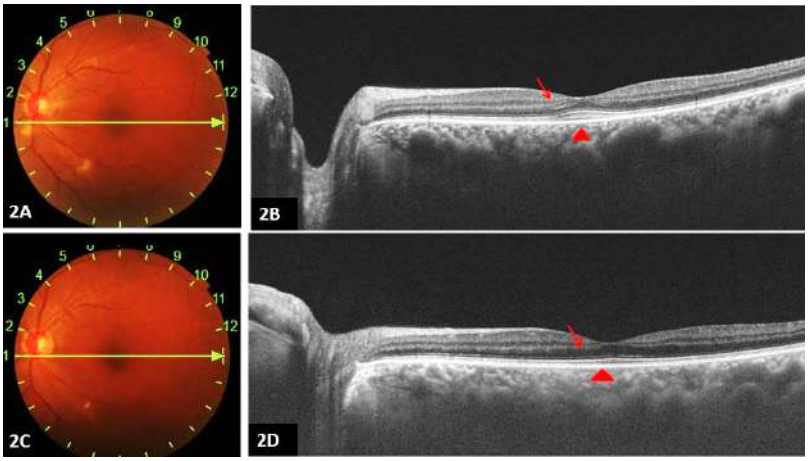

Figure 2:

2A) Colour fundus photography showing cotton wool spots slong superior and inferior vascular arcades.

2B) SS-OCT showing hyperreflective thickened outer plexiform layer (arrow) with streak of shallow subretinal fluid (arrow head).

2C) Colour fundus photography shows resolving cotton wool spots.

2D) shows resolved sub retinal fluid (arrow head) and normal outer plexiform layer (arrow).

CASE 2 :

A 45-year-old lady, diabetic since 6 years, presented with painless, decreased vision in RE since 3 days. She had history of COVID-19 related pneumonia 20days back, for which she was hospitalized for 1week and treated with oxygen for 3 days. She had received 3 doses of injection Remidesivir, oral steroids and anticoagulants for 20 days. At presentation, her BCVA in RE was 20/125 and 20/20 in LE. Abduction in RE was restricted, other ocular movements were normal .There was no proptosis, no facial or paranasal skin changes. RE showed Relative Afferent Pupillary Defect (RAPD), LE pupillary reflexes were brisk. Fundus was normal in BE (Fig 3A). RE OCT showed normal foveal contour with focal hyper-reflective band at the level of OPL and inner nuclear layer (INL) and merging of OPLwith inner plexiform layer(IPL) around the perifoveal region(Fig 3D) suggestive of PAMM. OCT-Angiography showed near normal superficial capillary plexus but the deep capillary plexus showed perifoveal areas of attenuated flow signals (Fig 3 B,C) corresponding to hyper reflectivity on OCT suggestive of PAMM.Because of presence of RAPD, PAMM and abduction deficit, an impending thromboembolic event secondary to obstructive lesion at orbital apex was suspected and she was advised MRI brain and paranasal sinuses .MRI showed sinusitis extending into ethmoid,sphenoidal sinuses and orbital apex (Fig 3E) suggestive of probable rhinocerebral mucormycosis. Patient was further referred to ENT surgeon for ethmoidectomy and sphenoidectomy .Histopathology of debrided sinus tissue revealed Klebsiella pneumonia.

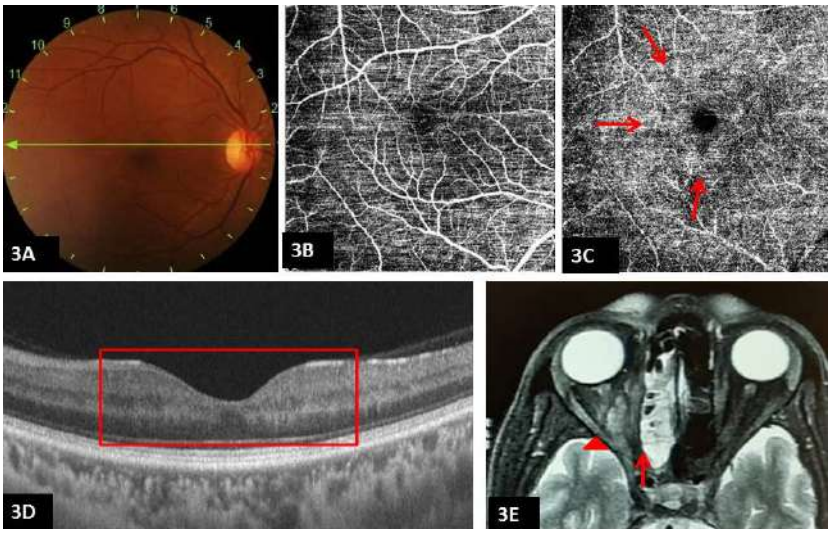

Figure 3: 3A)Colour fundus photography showing no abnormality .

3B)OCT Angiography, superficial capillary plexus showing near normal vascular signals.

3C)OCT Angiography, deep capillary plexus showing ill-defined perifoveal areas of attenuated flow signals(red arrows) .

3D)SS-OCT showing hyper reflective outer plexiform layer and inner nuclear layer in parafoveal area(red box)

3E)MRI brain T2 weighted image shows involvement of anterior and posterior ethmoidal sinuses (red arrow) with orbital apical congestion (red arrow head).

Discussion:

The full spectrum of COVID-19 disease is yet to be unraveled.Various retinal manifestations have been reported concurrently or following COVID-19 infection. In this report, we report cases that presented with AMN as initial manifestation of COVID-19 and a case with rhinocerebral klebsiella extending into orbital apex that presented with PAMM post COVID-19 infection.The association of AMN with febrile illness was established in 47.5% on studying 101 cases of AMN by Bhasvar et al.[4] OCT features of AMN include focal hyper reflectivity of OPL and ONL which is thought to be characteristic and early sign of AMN. Other features include disruption of external limiting membrane (ELM), IZ, EZ. These features were observed in our case along with a shallow neurosensory detachment.[5] Near infrared reflectance imaging can show grayish wedge shaped lesions and visual field analysis demonstrates paracentral scotomas correspondingly. Cause for AMN in our case was initially thought to be immune mediated secondary to vaccination but this was ruled out because of insignificantly raised antibody titers. AMN has been reported secondary to COVID-19 infection with raised D-dimer levels secondary to increased inflammatory markers causing a thrombotic milieu leading to retinal capillary plexus ischemia.[6] In our case D-dimer was normal. Presence of cotton wool spots in patient also reflects underlying ischemic pathophysiologic mechanism causing arteriolar hypoperfusion.[7]

PAMM was initially thought to be a novel variant of AMN,but is now considered to be two distinct conditions with overlapping findings.[8]PAMM occurs in association with reduced flow in intermediate, deep and occasionally in superficial capillary plexuses, whereas AMN occurs in association with reduced flow in the deep capillary plexus.[9] The immune complex deposition causing occlusion of pre capillary arterioles leads to deep and superficial capillary plexus ischemia leading to AMN and PAMM respectively.[7]Occurrence of PAMM in this patient was presumed to be due to orbital apex compression causing partial mechanical occlusion of ophthalmic artery explaining RAPD and occurrence of PAMM.

Conclusion

This would be the very first case report to show very early PAMM like lesions in cases of orbital apex compression secondary to rhinocerebral bacterial infection post COVID infection.

We would like to propose that all cases of history of febrile illness in the pandemic should get a thorough ocular examination and retinal imaging like OCT ,OCTA as they can give us some very significant insights into the associations of COVID -19 infection which could be so subtle and can be missed by bare clinical examinations. Presence of PAMM could be a prequel to more sinister complications like combined artery and vein occlusion and frank proptosis caused by secondary rhinocerebral bacterial infections or mucormycosis. Hence multimodal imaging helps saving life and vision.

AMN and PAMM in COVID indicate a compromised vascular supply warranting a complete evaluation.Also, this report demonstrates the role of an ophthalmologist in identification and timely referral of associated life-threatening conditions.

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Post COVID-19 Vaccination and unilateral branch retinal/ cilioretinal artery occlusion with venous stasis retinopathy

- Dr. Srinivasan Sanjay[1], Dr. Naresh Kumar Yadav[1], Dr. Ankush Kawali[1], Dr. Padmamalini Mahendradas[1]

[1]Narayana Nethralaya, Bengaluru, Karnataka

Abstract

A 52-year-old lady presented to us with blurring of vision (BOV) in her left eye (OS) of 1 month duration after COVID-19 vaccination. She had a history of supraventricular ectopic beat and known case of Hashimoto's thyroiditis and was on oral metoprolol 50 mg since 2017. OS was diagnosed with vein occlusion with macular edema and treated with intravitreal ranibizumab injection elsewhere. Best corrected visual acuity (BCVA) was 20/20 in right eye and 20/80 in OS. Anterior segment was normal. OS fundus showed multiple cotton wool spots, flame shaped hemorrhages in superior and infero nasal quadrants, with resolving exudates in macula. A clinical diagnosis of combined branch artery occlusion possibly with cilio retinal artery occlusion and vein stasis retinopathy in OS was made. Women may have a pre-ponderance for clotting which may be autoimmune mediated. Occurrence of retinal vascular events is not a deterrent for COVID-19 vaccination.

Keywords : COVID-19 vaccination; Branch retinal artery occlusion, venous stasis retinopathy, macular edema; Anti VEGF

limb swelling on the same day. Two days later she had fever with chills and BOV in her OS. Unfortunately the details, batch, dose of the vaccine were not available to us. Clinical evaluation of the cardiovascular system and other systems were normal. Evaluation at a local hospital, showed her best corrected visual acuity (BCVA) of OS was counting fingers at 2 metres; right eye (OD) was 20/20. At the local hospital in her country, she was diagnosed to have left supero-temporal branch retinal vein occlusion and was given a single dose of intravitreal ranibizumab injection and was referred to a higher centre.

The fundus photo which was available with the patient, done at the local hospital showed multiple areas of infarct in the supero-temporal macula. Based on this picture our likely diagnosis was cilio-retinal/branch retinal artery, venous stasis retinopathy with macular oedema in the OS. Figure 1

Introduction

Ophthalmic manifestations including retinal vascular events like acute macular neuroretinopathy, paracentral middle maculopathy, retinal vascular occlusions have been described with COVID-19 vaccination.[1,2] We describe a patient with unilateral combined branch artery occlusion with venous stasis retinopathy and macular edema 2 days after the COVID-19 vaccination.

Case report

A 52-year-old Asian female from a neighbouring country presented to us with blurring of vision (BOV) in her left eye (OS) of 1 month duration. She had a history of Supraventricular Ectopic Beat (SVE) and Hashimoto's thyroiditis and was on oral metoprolol 50 mg since 2017 with no complications resulting from it. In the month of February 2021 she had vaccination for Corona virus disease (COVID-19) following which she developed upper

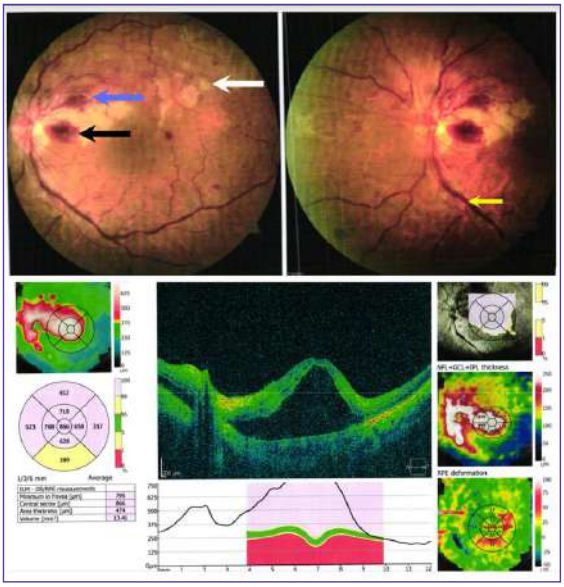


Figure 1 (Top) colour fundus photograph done elsewhere showing haemorrhages in all quadrants (blue arrow) with disc hyperaemia, dilated tortuous blood vessels (yellow arrow), cotton wool spots, opacification of retina (infarcts) (white arrow) and macular oedema

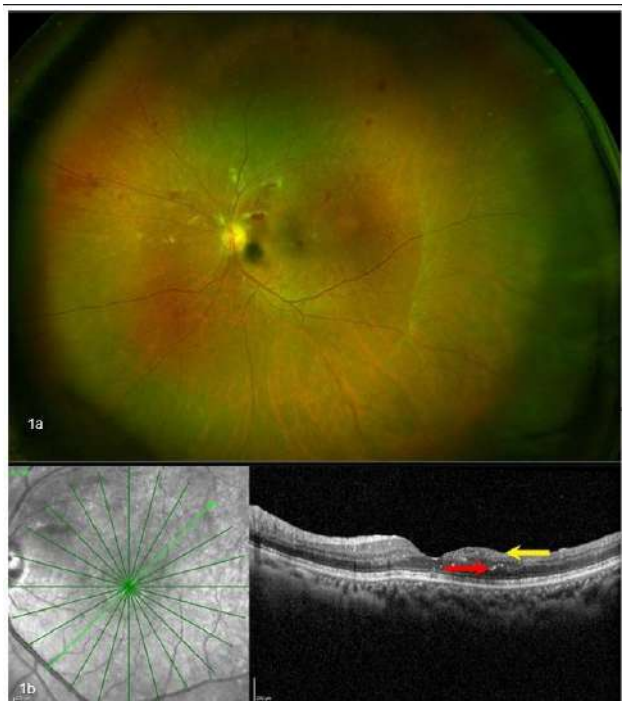
Figure 1 (Bottom) Optical coherence tomography of the left eye (LE) showing disorganisation of inner retinal layers with sub retinal fluid.Figure1was obtained with patient's consent and was done elsewhere.Based on this picture our likely diagnosis would be a cilio-retinal/branch retinal artery with venous stasis retinopathy.

On evaluation at our centre BCVA was 20/20 in OD and 20/80 in OS. Anterior segment examination was normal in both the eyes. OS fundus showed multiple cotton wool spots, flame shaped haemorrhages in superior (nasal and temporal) and infero-nasal quadrants, with resolving exudates in macula. (Figure 2a)

Spectral domain optical coherence tomography (SD-OCT) (Figure 2b) showed disorganisation of inner retinal layers with thinning and hyper reflective spots in the middle layers with a normal foveal contour.

Figure 2a Widefield colour fundus photograph with Optos™ of the OS showing haemorrhages in the supero temporal, nasal and inferonasal quadrants, cotton wool spots in superior and inferonasal quadrants, fine exudates in the macula near fovea

Figure 2b Spectral domain optical coherence tomography of the OS showing disorganisation of inner retinal layers with thinning(yellow arrow) and hyper reflective spots in the middle layers(red arrow) with a normal contour.



Multicolour imaging with Spectralis™ (Figure 3) showed in the composite multicolour image greenish hue in the macula indicating a resolving oedema with greenish dots and haemorrhages. Blue and green reflectance showed haemorrhages as darker areas and hyper-reflective area around the fovea.Fundus fluorescein angiography was suggested to the patient, but she declined the option.

Figure 3 Multicolour imaging with Spectralis™ showing the composite multicolour image greenish hue in the macula indicating a resolving oedema with greenish dots (exudates) (red block arrow) and haemorrhages.Blue and green reflectance show haemorrhages as darker areas (red hollow arrow) indication inner and middle retinal layer involvement and hyper-reflective area around the fovea.

Discussion

Viral vector vaccines have been reported to lead to venous thrombotic events. However, it is a matter of debate whether thromboembolic events occur in a higher frequency after the use of RNA vaccines as some studies have reported such events and while others did not.

Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) is a recently recognised syndrome observed in a small number of individuals who received the ChAdOx1 CoV-19 vaccine and was first identified in March 2021. The main features are thrombocytopenia and thrombosis within 5–30 days of adenoviral SARS-CoV-2 vaccination, with markedly elevated levels of D-dimer and presence of anti-PF4 antibodies.[5]

Girbardt et al [4] reported 6 cases of retinal vascular events after COVID-19 vaccine. Their series included 6 patients with 4 males and two females. 3 had the event after 1st dose and 3 after the second dose. The duration to event was between 2- 12 days. The diagnosis in their series included branch artery occlusions, combined artery/venous occlusions, non-arteritic anterior ischaemic optic neuropathy, cotton wool spot, left venous stasis retinopathy and acute macular neuro retinopathy.

COVID-19 vaccination can be associated with

thromboembolic events with adenovirus vector-based vaccines and also can be associated with systemic inflammation, platelet and endothelial dysfunction.[5] Two patients who developed central retinal vein occlusion (CRVO) after mRNA based COVID-19 vaccine have been recently reported.[6,7]

A 74-year-old woman presented with painless vision loss in the right eye experienced 48 hours after receiving a second dose of the mRNA-1237 vaccine [8] and was diagnosed with retinal vein occlusion which is similar to our patient but without branch artery occlusion. Bollletta et al reported AMN, retinal vein occlusion (RVO), and non-arteritic ischemic optic neuropathy (NAION) in their series of patients.[9]

Further multicentre longitudinal studies are required to analyze whether a direct association exists between the vaccine and the thrombo embolic event.

We herein report a female patient with of retinal vascular occlusion/ venous stasis retinopathy with macular edema after COVID-19 vaccination which may be a temporal association rather than causal. Occurrence of retinal vascular events is not a deterrent for COVID-19 vaccination.

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Septicemia Induced Bilateral Exudative Retinal Detachment With Choroidal Detachment

- Dr. Hegde Sharat Shivaramaiah[1], Dr. Gunashree K N[1],
[1]Prasad Netralaya Superspeciality Eye Hospital, Udupi

Abstract

A young male patient presented with sudden onset diminution of vision in both eyes since 1 week with bilateral multiple exudative retinal detachments and choroidal detachment. The patient had a history of fever for 1 week and was recently diagnosed as having HIV with a CD count of 73 cells/mm . Systemic and ocular investigations were done to find out the etiology and Urine culture came positive to E.*coli*. Appropriate systemic intravenous antibiotics were started with topical steroids, antibiotics and cycloplegics. The exudative retinal detachment and choroidal detachment recovered gradually over time without ocular surgical intervention. We report a case of septicemia induced bilateral exudative retinal detachment with choroidal detachment.

Keywords: Septicaemia, choroidal detachment, retinal detachment, HIV

Introduction

Exudative retinal detachment can be due to various etiologies including inflammatory conditions (VKH, posterior scleritis), neoplastic etiologies (choroidal melanoma and choroidal metastatic lesions), and idiopathic etiologies such as uveal effusion syndrome. Having Exudative retinal detachment with choroidal detachment is an extremely rare condition. Here reporting a case report of exudative retinal detachment with choroidal detachment due to an infectious cause is rarely seen which leads to diagnostic dilemma.

Case presentation

A 33 Year old male patient presented with sudden onset diminution of vision in both eyes for 1 week. The patient was admitted elsewhere for high grade fever, vomiting from the past 1week and referred to our center for his visual complaints. His initial systemic work up was positive for HIV and was negative for typhoid, malaria, leptospira, dengue antigens. A further confirmatory ELISA test and CD4 cell count was sent to confirm his immunocompromised status which confirmed his retro positive status with CD4 cell count of 73. The patient was not diabetic, hypertensive.

On examination the patient's visual acuity at presentation was Counting fingers at 1metre in both eyes. His intraocular pressure in the right eye and left eye was 24 and 22 mm Hg respectively. Anterior segment examination in the right eye revealed AC flare of +4 with a fibrinous contracting pupillary membrane with few posterior synechiae. The left eye had no ac cells/flare with a well dilating pupil. Both eyes had clear lens. Right eye had +1 Retrolental cells. Fundus examination in both eyes had very few flame shaped hemorrhages in the posterior pole with multiple neurosensory detachments with outer retinal whitish lesions with choroidal detachment in 3 quadrants. (Figure 1) Fundus fluorescein angiography showed early hypo fluorescent lesions with late pooling with no evidence of neovascularization with disc leakage (figure 2). OCT revealed multiple neurosensory detachments in both eyes involving the fovea (Figure 3).

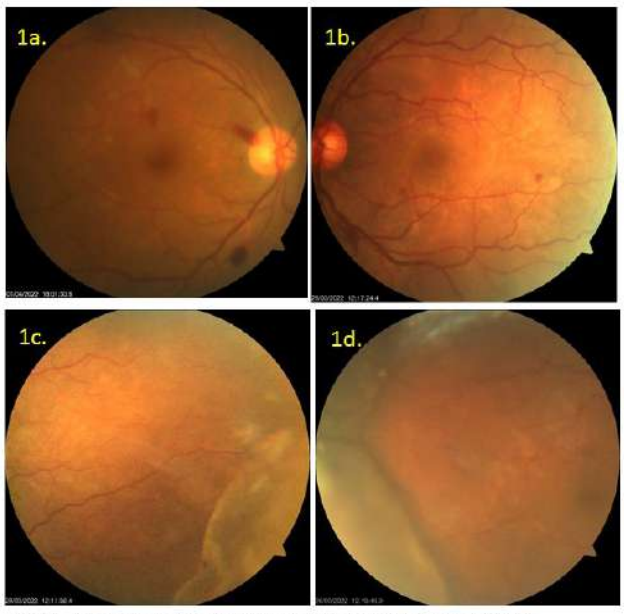
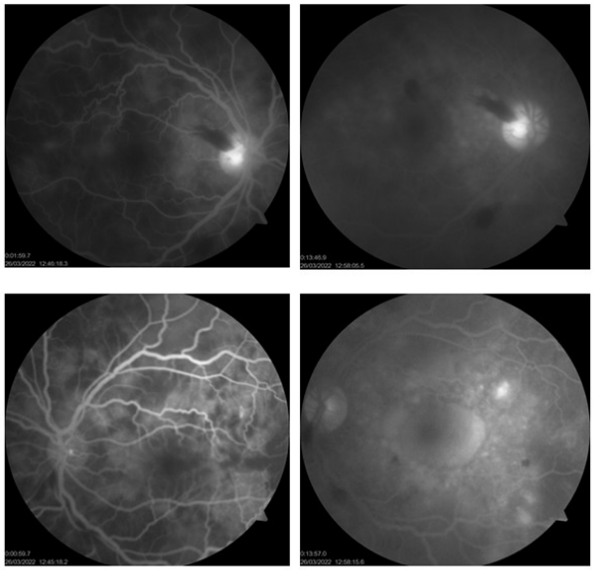


Fig 1a, 1b -Fundus photo of Right eye and Left eye showing multiple neurosensory detachments. Note the outer retinal whitish lesions with few intraretinal hemorrhages in both eyes. Fig 1c, 1d- showing areas of choroidal detachments in both eyes.

Figure 2



Early and late phases of FFA of Right eye(top row) and Left eye(bottom row) showing early hypofluorescent patches with late pooling. In the Left eye, late pin-point hyperfluorescent lesions were also seen.

Figure 3

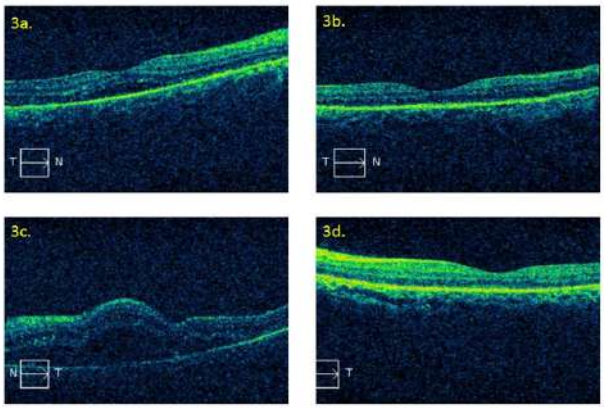


Figure 3a , 3c showing OCT of RE and LE respectively, at presentation showing multiple neurosensory detachments. Figure 3b, 3d showing the 4th week follow up OCTs of RE and LE respectively , where neurosensory detachments have resolved completely.

With further investigations, he was TPHA negative, his blood culture showed no growth, but the urine culture showed Escherichia coli growth of >10^5 CFU/ml. He underwent chest X-ray, Mantoux to rule out tuberculosis which was negetive. Complete blood picture revealed increase in neutrophil cell count, peripheral blood smear was normal. A clinical diagnosis of Bilateral choroidal detachment with retinal detachment secondary to septicaemia was made based on above findings.

Based on the sensitivity report, *E. coli* isolated from the urine culture was sensitive to Ceftriaxone. Hence intravenous Ceftriaxone 1g, 12th hourly with topical steroids (prednisolone acetate 6 times a day), topical cycloplegics (Homatropine 3 times a day)were started.

Three weeks after initial presentation, his vision had significantly improved to 6/36 and 6/9 in the right eye and left eye respectively and IOP was 12 and 11 mm Hg in the right and left eye respectively. The anterior segment inflammation, choroidal detachment had completely resolved and neurosensory detachments in both eyes were resolving.

Discussion

Endophthalmitis leading to sight threatening complications is a well known entity in patients with septicaemia. Septicaemia has other sight threatening ocular complications also such as ciliary body shut down, sterile panuveitis in response to the antigens of the offending pathogen etc. Severe ocular hypotony can occur acutely following cardiogenic shock.(1) Our patient was admitted in the ICU for 3 days , following several episodes of Vomiting and high fever. The acute severe dehydration or septicaemia perse might have led to a state of shock and hence ciliary body hypoperfusion, which led to a state of ocular hypotony. The choroidal and multiple neurosensory detachments could be the sequelae of the acute ocular hypotony. Also being recently diagnosed as immunosuppressed condition may lead to ocular involvement of septicaemia.

The increased neutrophil count on complete blood count and normal peripheral smear also gave a clue to an infective etiology and excluded neoplastic and non-neoplastic masquerade syndromes. Behcet's disease, Vogt Koyanagi Harada's disease, were ruled out based on the clinical appearance and significant history of fever, hospitalisation and culture positive urinary tract infection.

The patient had already been treated with broad spectrum systemic antibiotics. This could be the reason why his blood culture was negative for microbial growth on culture. But the positive urine culture with significant E.coli growth of >10^5CFU/ml , past high-grade fever that responded to parenteral antibiotics and the significant neutrophil count on complete blood analysis , gave a clue towards a systemic infection that was responsible for the bilateral ocular manifestations. Similar findings were reported by Rani PK. *et al*(2) where culture positivity was proved by vitreous biopsy following vitrectomy for the choroidal and retinal detachment. Serous choroidal detachment due to infectious etiology has also been described. [3]

Conclusion

In an immunosuppressed patient, with sudden onset diminution of vision following fever with bilateral choroidal and retinal detachments, a high index of suspicion of a septicaemia must be kept in mind. Appropriate systemic evaluation to find out infective foci, and timely systemic antibiotics with topical steroids to control inflammation can help to save vision.

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Topiramate Induced Bilateral angle-closure Glaucoma

- Dr Sangita kakade, [1]Dr Maneesh Bapaye,[1]
Dr Charuta Bapaye ,[1] Dr Meena Bapaye[1]
Dr Bapaye Hospital, Eye care center, Nashik, Maharashtra

Abstract:

Topiramate is an oral sulfamate substituted monosaccharide still widely used in pediatric and adult patients for the treatment of seizures, migraine headaches. It has also demonstrated efficacy for the treatment of bipolar disorders, weight loss, and de-addiction of alcohol. Topiramate is a well-known cause of drug-induced bilateral angle-closure glaucoma. We present a case series of three patients with topiramate-induced angle-closure glaucoma. Early detection and withdrawing medication are very crucial along with supportive treatment to counteract the drug-induced side effects of angle-closure caused by ciliochoroidal effusions and myopic shift, anterior uveitis, or panuveitis. Laser iridotomy or anterior vitrectomy has no role in this angle-closure glaucoma.

Keywords: Topiramate, Angle-closure glaucoma, Ciliochoroidal Effusion, Myopic shift, Anterior uveitis. Panuveitis, Iridotomy, Vitrectomy.

Key Messages: It's essential to take appropriate history of recent addition of Topiramate which is still prescribed by many physicians and psychiatrist's when a patient presents with acute attack of bilateral angle closure glaucoma. We need to withdraw this medication and avoid laser iridotomy or vitrectomy to save the vision

Introduction:

Topiramate was approved for medical use in the United States in 1996[1]. In March 2011, the FDA notified health care professionals and patients, regarding congenital anomalies in infants when used during pregnancy and placed it in pregnancy category D[2,3]. Banta et al first reported a case of uveal effusion associated with Topiramate use in July 2001[4]. Fraunfelder et al reported the largest series in 2004 describing ocular side effects of Topiramate in 115 patients out of which seven patients were reported with permanent vision loss[5]. It indicates the need for awareness regarding the potential threat of sight loss while using this drug. Neurologists, physicians, psychiatrists can inform the patient regarding its ophthalmic side effects and ask them to report immediately to an ophthalmologist in case of any visual disturbance. Depending on the side effects caused by the drug, we can treat the patient with the help of oral carbonic anhydrase inhibitors or iv mannitol, cycloplegics, topical antiglaucoma medications, topical or systemic steroids after withdrawing topiramate promptly.[6,7,8]

Case 1:

A 46-year-old male presented with symptoms such as swelling of eyelids, watering, photophobia, decreased vision, and headache for over three days. The previous examination revealed no ocular abnormality. He was emmetropic with presbyopic glasses. Past medical history was not significant. His body weight was 56 kilograms. He had recently been added on with tab Topiramate 25mg bd along with his old antiepileptic medication (Tab Valprol CR) one week before this visit.Ocular examination revealed moderate ciliary congestion. The pupil was semi dilated fixed with fibrin over the anterior lens capsule with Descemet's folds in the cornea in both eyes. Anterior chambers were very shallow, gonioscopy revealed grade zero angles by Schaffer's classification in all quadrants in both eyes. The B scan of both eyes was within normal limits. Visual acuity was 1/60 in both eyes with no pinhole improvement. Goldmann Applanation Tonometer (GAT) showed 20mm of hg in the right eye and 24 mm of hg in the left eye. The patient was diagnosed with topiramate-induced bilateral anterior uveitis with secondary angle-closure glaucoma.

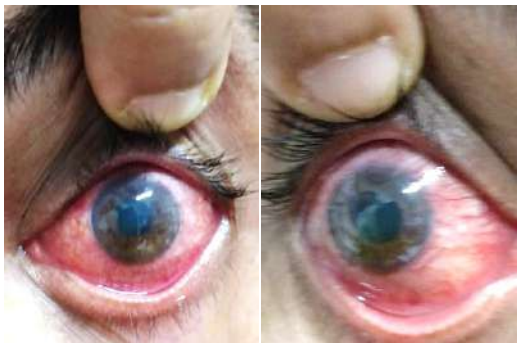

Fig 1,2 - Bilateral Acute Angle Closure Glaucoma

Tablet Topiramate was discontinued and the patient was started with oral acetazolamide and steroids, 2%topical atropine TDS, timolol maleate 0.5% bd, prednisolone acetate QID. At the end of two weeks, gonioscopy showed open angles grade four in all quadrants and visual acuity was 6/6 in both eyes with Intraocular pressure (IOP) 12 on GAT in both eyes. Visual acuity was stable and IOP remained in the normal range after the withdrawal of topical medications over the latter two months.Careful clinical evaluation and history enabled accurate diagnosis of this case.

Case 2:

A 24-year-old female patient presented symptoms such as blurred vision, severe headache, and nausea. The previous examination revealed myopia of -1.5 D in both eyes with 6/6 vision. She had been given an oral Topiramate 25 mg at night for the last eight days for migraines.On examination, she was found to have a myopic shift of -4.0 D with 6/18 vision in both eyes. Both eyes had clear cornea with grade 0 angle closure in all quadrants opening on manipulation by Schaffer's classification which was confirmed on the Anterior Segment Optical Coherence Tomography (AS-OCT). IOP was 46 mm of hg in the right eye and 52 mm of hg in the left eye. The posterior segment and optic nerve were within normal limits. A diagnosis of Topiramate-induced bilateral acute angle-closure was made based on that observation.

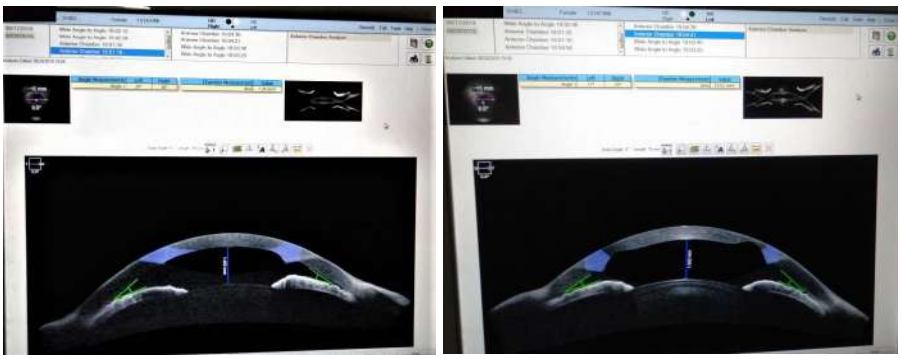

Fig 3,4 - Anterior Segment OCT - Before Treatment

Topiramate was stopped and she was managed with oral and topical antiglaucoma medications and topical cycloplegic and steroids. Follow-up after one week showed IOP within normal limits and reversal of myopic shift. AS-OCT showed improvement in anterior chamber depth. At the end of two weeks, gonioscopy revealed wide-open angles without any synechia.

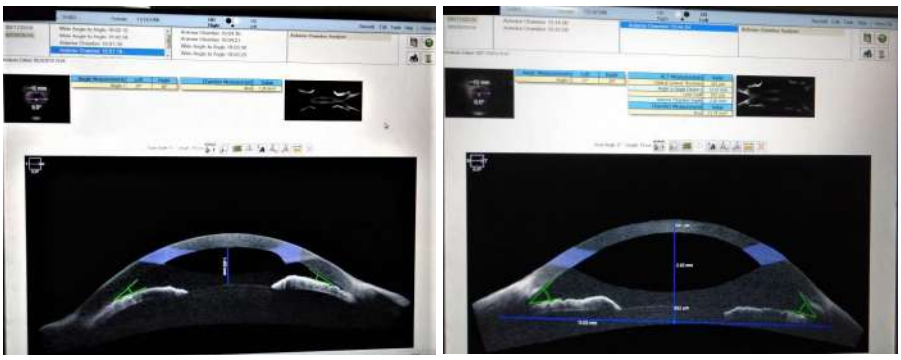

Fig 5,6 - Anterior Segment OCT - After Treatment

Follow-up at the end of two months after stopping all medicines was normal.

Case 3:

A 42-year-old female with complaints of acute headache, pain in both eyes, and congestion with a history of the oral tablet Topiramate 25mg BD for one week was found to have ciliary congestion with microcystic corneal edema and a very shallow anterior chamber. Non-Contact Tonometer (NCT) showed an error and GAT or gonioscopy was not performed as it was painful for the patient. Digitally the eyeball was hard. Her vision was of two to three feet in either eye. She was advised intravenous mannitol with oral acetazolamide and topical steroids, cycloplegic and antiglaucoma medication with immediate withdrawal of tablet topiramate. Unfortunately, she was unavailable for a follow-up and reported back after three months.She had undergone iridotomy followed by an anterior vitrectomy elsewhere, in both her eyes and post which she had lost her vision.

Discussion:

The above cases highlight the awareness of sight-threatening side effects of this drug and the need to promptly withdraw the drug to avoid permanent blindness. It also shows the adverse effects of iridotomy or vitrectomy in this drug-induced bilateral angle-closure disease. We should take a history of the recent addition of such medications before treating such patients. Also, we should make an effort to create awareness about the side effect of this drug amongst physicians and psychiatrists.

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Conflicts of interest: None

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How to approach a child with double vision

- **Dr. Smitha BT**
Postgraduate, Department of Ophthalmology,
Basveshwara Medical college, Chitradurga.

Diplopia in the pediatric population can be a diagnostic challenge, and it is important to understand because several life-threatening conditions can present as diplopia. Part of the challenge lies in the fact that not all pediatric patients will complain of diplopia in the classic sense, especially younger patients. Younger patients may display nonspecific changes in behaviour such as perceived clumsiness, inability to perform previously mastered motor skills, or frustration/agitation with visual-motor tasks. Patients < 18 months generally will not experience diplopia in the presence of ocular misalignment because of rapid neurological adaptation and resulting suppression of the deviated eye. Older children with chronic ocular misalignment also will not experience diplopia for the same reason. Therefore, a child complaining of diplopia will likely be preschool age or older and have an acute onset of symptoms. Another possible presentation would be parents bringing their child because they have noticed a new eye deviation, or abnormal head position or see that their child is closing one eye.

The 3 most important initial questions are as follows:

1. What was the acuity of onset?

2. Is the diplopia monocular or binocular?

3. Is the diplopia horizontal or vertical?

Acute Versus Chronic

Acuity of onset is important because acute diplopia often warrants an expedited work-up and immediate referral to the appropriate specialists. As mentioned above, a child with a chronic ocular misalignment usually does not experience diplopia; therefore, the simple fact that a child is complaining of diplopia usually implies an acute onset. Causes of acute binocular diplopia are listed in Table 1 and include cranial nerve palsies, orbital mass lesions, orbital inflammations/infections and diseases affecting the extraocular muscles. Chronic ocular misalignments in children more commonly represent a primary strabismus and call for a nonurgent referral to an ophthalmologist. Also, ocular misalignments manifesting within the first 6 months of age (in the absence of other findings) usually represent a primary strabismus and can be referred to ophthalmology within a few weeks (sooner than older children because the consequences of ocular misalignment on visual development progress more rapidly in the infant population).

Differential Diagnosis of Acute Binocular Diplopia

Cranial Nerve Palsies (III, IV, and/or VI)	Orbital Disease	Muscular and Neuromuscular Disease
Intracranial infection (encephalitis, meningitis)	Rhabdomyosarcoma	Inferior rectus entrapment following floor fracture
Intracranial mass	Capillary hemangioma	Complications following eye muscle surgery
Increased intracranial pressure	Dermoid cyst	Orbital myositis
Head trauma (CN IV>VI>III)	Lymphoma	Botulism
Post-viral (usually CN VI)	Metastatic disease	Guillain-Barré syndrome (Miller Fisher variant)
Severe otitis media with mastoiditis (CN VI)	Infection and inflammation	Myasthenia gravis (rare in children)
Posterior communicating artery aneurysm (CN III)	Orbital cellulitis +/- subperiosteal abcess	Muscular dystrophies
Uncal herniation (CN III)	Thyroid eye disease (Graves' disease)	Some metabolic diseases
Multiple sclerosis	Orbital pseudotumor	
Hypertensive emergency		
Cavernous sinus thrombosis		
Migraine headache (rare)		

Abbreviation: CN, cranial nerve.

Monocular Versus Binocular

Monocular versus binocular diplopia is important to elucidate because the etiologies of the 2 groups are different. Monocular diplopia represents non-life-threatening (but potentially sight threatening) conditions, whereas binocular diplopia should raise a red flag. The child and/or parents usually will not volunteer this information, but it is easily determined in the office. Have the child cover one eye and ask if he or she still has double vision. Repeat the test for the other eye. If the diplopia continues with one eye covered, it is monocular. If the diplopia resolves with either eye covered, it is binocular. It is important to test both eyes because monocular diplopia will resolve with one eye covered if the covered eye is the one with pathology. If the child complains of seeing more than 2 images, this indicates a monocular etiology as well. Alternatively, Hirschberg's test can be used as an objective way to determine ocular alignment in a child

brought in because of an eye deviation noted by the parents or one of the behaviour changes described above. With the child fixating on a light source, the position of the corneal light reflexes is noted. When the light reflexes are centered over both pupils, alignment is normal. If the light reflex is centered over one pupil but not the other, a misalignment is present. Caution should be used in declaring the eyes to be straight by this method because small deviations are easily missed even by an experienced observer. Monocular diplopia implies a primary ocular etiology such as corneal abrasion, other corneal surface irregularities, polycoria (multiple openings in the iris other than the pupil), lens opacities, lens dislocation, or certain retinal pathologies (Table 2). Binocular diplopia implies a disorder of ocular alignment caused by cranial nerve palsy, orbital mass, orbital inflammations/infections, and diseases affecting the extraocular muscles and necessitates more urgent work-up.

Horizontal versus Vertical

If the diplopia is binocular in nature, it helps to further classify the symptoms as horizontal orvertical. In monocular diplopia, this further classification is somewhat irrelevant. Simply ask the patient if the 2 images are seen mostly side by side or mostly one on top of the other. Sometimes there will be a pause and a response like, “One is over here and one is over there,” while pointing to objects in a diagonal orientation. If this is the case, try to prompt the patient to decide whether the more prominent component of his or her diagonal diplopia is—horizontal or vertical.

Differential Diagnosis of Monocular Diplopia

- Corneal abrasion
- Other corneal surface irregularity
- Polycoria (multiple openings in iris)
- Lens dislocation
- Severe dry eye
- High astigmatism
- Lens opacity (cataract)
- Some retinal pathology

Horizontal diplopia can be caused by a cranial nerve VI palsy, which is accompanied by limitation of abduction of the affected eye. This is in contrast to an acute primary horizontal strabismus, which will have full range of motility. Cranial nerve III palsy will produce a primarily horizontal diplopia (although concurrent with a smaller vertical component) and is accompanied by limitation of adduction, elevation, and depression of the affected eye. Cranial nerve III palsy is also variably accompanied by ptosis and pupil dilation. A pupil-involving third nerve palsy is an emergency requiring urgent neuroimaging and should be considered secondary to an intracranial aneurysm until proven otherwise. Remember that if ptosis obscures the visual axis in a cranial nerve III palsy, no symptoms of diplopia will be present. Internuclear or supranuclear lesions such as those seen in demyelinating disease can also cause horizontal diplopia.

Vertical diplopia can be caused by a cranial nerve IV palsy and is much more subtle than cra-nial nerve III and VI palsies. Most patients with an acute cranial nerve IV palsy will present with a head tilt to the side opposite the palsy to eliminate their diplopia. Limitation of vertical eye movement is not prominent. Trauma resulting in an orbital floor fracture can occasionally lead to entrapment of the inferior rectus muscle and a restriction of elevation. This restriction is usually considerable and may be accompanied by vagal symptoms such as nausea/vomiting and bradycardia, as opposed to the smaller limitations of eye movement produced by large, swollen eyelids that accompany blunt trauma. Demyelinating disease such as multiple sclerosis can also lead to lesions causing vertical diplopia. Many other conditions will variably produce horizontal, vertical, or oblique diplopia. Orbital mass lesions (and sometimes eyelid lesions) that are large enough to displace the eyeball will produce diplopia with an orientation dependent on the direction in which the globe is pushed. Careful observation of the position of one globe relative to the other (Is there proptosis? Does one eye sit higher or lower than the other?) is important, and if abnormalities are present, they require orbital imaging. Orbital cellulitis can inflame any of the extraocular muscles causing vari-able limitations in motility. Sometimes it will lead to a subperiosteal abscess which in turn can produce mass effect on the globe. Intracranial infections (meningitis, encephalitis, abscess) and mass lesions can cause various cranial nerve palsies. Demyelinating disease can cause any type of cranial nerve palsy. Cavernous sinus thrombosis, large pituitary tumors, and mass lesions at the orbital apex can cause multiple concurrent cranial nerve palsies. Other inflammatory processes, such as thyroid eye disease and orbital myositis, can inflame any of the extraocular muscles and lead to muscle fibrosis and restriction over the long term. Neuromuscular junction disorders, such as myasthenia gravis, botulism, and Guillain-Barré syndrome (Miller Fisher variant), can cause variable diplopia and often first present with ocular findings. Muscular dystrophies can occasionally lead to diplopia as well.

Conclusion

A systematic approach to the child complaining of double vision is crucial. The main decisions that need to be made are the timing of appropriate specialist referrals and whether imaging is required. In general, acute presentation and binocular nature of diplopia are red flags that require a high degree of suspicion for serious underlying pathology. Subacute presentation is less concerning. Monocular diplopia involves only primary ocular causes but still may necessitate prompt referral because some sight-threatening conditions are associated. The horizontal versus vertical nature of diplopia can help narrow the differential diagnosis.

Financial Planning for Doctors & how it's different

The medical profession is held in awe and respect across the globe. It is a noble profession as doctors try to heal sickness, diseases, treat physical and mental trauma.

- **Mr. Alpesh Jain,**
Financial advisor,
Belgaum, Karnataka

✦ Doctors love Real Estate

Many doctors in India invest in real estate for housing and setting up a practice. They are generally overweight in real estate which might not be a good idea. They have to understand real estate is one of the asset classes – so there will be periods of outperformance & underperformance.

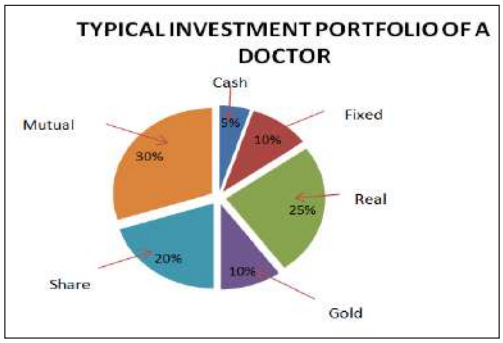
Doctors should take the following steps to ensure that their finances are in a good condition-

1. They should not be tempted to splurge once they start earning money. Some of them feel they missed out on opportunities to have fun as they spent many years studying and started to earn well much later in life. They splurge on fancy vacations, new cars, eating out etc. It is important to keep a check on expenditure and concentrate on savings and investments.
2. They should ensure that they have adequate life cover and disability insurance cover so that the financial needs of family and profession are taken care of in case of unfortunate events
3. Decent indemnity coverage is a must.
4. Doctors have a very busy schedule. They are also called in for work many times post-work hours. Apart from this, they have to manage family, health, social engagements etc. It is important that they have a proper fitness schedule. They have to eat right and exercise so that they are in good physical shape. They need to switch off from their work every day for some time and pursue what they like so that they are mentally fit. This is important for sound financial health.
5. They have to make a financial plan the plan should have financial goals listed and they should execute the plan to achieve these goals. If they do not have time to research and make one, they should hire the services of a financial planner. [hope doctors understand importance of professionals] They need to have a proper investment plan. They should invest in a variety of assets including equity, mutual funds and debt so that their investment portfolio is diversified and they get optimum returns and long-term capital appreciation. They should ensure that their debts are not beyond their means.

✦ Lack of financial literacy in Doctors: (harsh reality)

All doctors are incredibly dedicated and perfectionists in everything they do in their profession. But when it comes to handling finance, they just tend to follow their peers.

As a doctor, you might be an expert in your respective field. However, financial investments might be new and confusing when you are a complete beginner. This lack of knowledge could potentially lead you to fall prey to scams. In that case, it would be wise to seek advice from a financial advisor who as a professional can better guide you in this aspect. Just like how prescribed medicines work much better than the medicine you get over the counter, it is exactly how seeking financial Advise



Conclusion:

Financial health & physical health are interrelated. A better financial practice helps to achieve both financial well-being & physical well-being.

If your profession demands a lot of time & energy, then you may find it difficult to pay attention to your financial health. In that case, it will be wise to outsource it to finance professional.

Best Investment Options

- **Mr Kiran patil,**
Charted accountant, Davanagere, Karnataka

We are all aware of how important it is to consider our own investment options. A financially secure life must, however, also include money accumulation and returns that can improve the future and your goals. Additionally, relying solely on savings won't always make sense, will it?

There are plenty of investing options in India. In this article, you will find out what you would like to opt for to create financial stability and security that would benefit you. So here, based on three main criteria, you can choose how you could start your investment journey:

- **Low-Risk Investments**
- **Medium-Risk Investments**
- **High-Risk Investments**

What is A Low-Risk Investment?

Simply put, a Low-Risk investor is one who has a lower risk tolerance. It indicates that the investor wants little to no volatility in their portfolio of investments.

Typically, retirees and beyond who have spent years building a nest egg choose to make these investments. The returns from these investments are always guaranteed because they rely on fixed-income instruments.

Here Are A Few *Low-Risk Investment Options*

1. Fixed deposit

They are consistently regarded as one of the best investment options and the safest form of investment. You can assemble high returns from various Fixed Deposit schemes through a fixed deposit. The fund always maintains security and promises returns free of market fluctuations. Most importantly, the principal on a fixed deposit is not depreciated.

2. Public provident fund

A Public Provident Fund is a government-backed investment option that can be used for a safe investment with high returns in India. It provides you with a risk-free return, which also makes it one of the best investment options. The interest that is received over the amount on this scheme is revised and paid by the government every quarter.

3. Money market funds

Money Market Funds are short-term debt funds. They invest in various money market instruments and endeavour to offer good returns over a period of up to one year while maintaining high levels of liquidity. The average maturity of a Money Market Fund is one year.

4. Municipal bonds

A Municipal Bond or Muni-Bond is a debt instrument issued by municipal corporations or associated bodies in India. These local governmental bodies utilize the funds raised through these bonds to finance projects for socio-economic development through building bridges, schools, hospitals, providing proper amenities to households, etc.

5. Certificate of deposit

A Certificate of Deposit is a term deposit that is offered by scheduled commercial banks which do not have the option of premature redemption. The primary difference between a Certificate of Deposit and a Fixed Deposit is that a Certificate of Deposit is freely negotiable.

6. Treasury bills

The Government of India issues Treasury Bills to raise funds for a period of up to 365 days. It is considered an investment with best returns. Since these are issued by the government, they are considered to be very safe. However, lower risks also translate into lower returns which is the case with treasury bills too. The returns on Treasury Bills are lower than other money market instruments.

What is A Medium-Risk Investment?

Some investors are quite comfortable with Medium-Risk investments on the table. These returns are relatively higher when compared to low-risk investments. They are the investments that have a certain level of risk, but at the same time, they hold higher returns.

Here Are A Few Medium-Risk Investment Options

1. Balance mutual funds

A Balanced Mutual Fund is another one of the most prominent investment options in India and even though it is subjected to market risks, it can be the best investment to grow money multifold. When you have a lower risk appetite but want higher returns, a fixed income mutual fund or monthly systematic investment plan can be your best investment option.

2. Debt funds

Debt Funds are mutual funds that invest in fixed-income securities such as bonds and treasury bills. These have monthly income plans, or so that assure some sort of locked-in money and not a total loss. They definitely have a low-risk ratio when compared to high-risk investments.

3. Dividend-paying stocks

Dividend-Paying Stocks are an excellent way to invest in the stock market. Although they're not as popular as high-yield bonds, dividend-paying stocks offer investors a way to earn a steady income from their investments. They're also known as "blue chip" stocks, because of their history of paying dividends and the fact that they tend to be bought by institutions such as mutual funds and pension funds.

4. *Exchange traded funds* (ETFs)

An ETF, short for Exchange-Traded Fund, is just like a stock and can be also called a basket of securities that also trade on the stock market.

Exchange-traded funds pool the financial resources of several people and use them to purchase various tradable monetary assets such as shares, and debt securities such as bonds and derivatives. Most ETFs are registered with the Securities and Exchange Board of India (SEBI). It is an appealing option for investors with limited expertise in the stock market.

5. Corporate bonds

A Corporate Bond fund is essentially a mutual fund that invests more than 80% of its total financial resources in corporate bonds. Business organizations sell these to fund their short expenses, such as working capital needs, advertising, insurance premium payments, etc. Corporate bond funds are increasingly becoming a popular debt instrument for businesses to raise required finances as associated costs are lower compared to bank loans.

What is A High-Risk Investment?

A High-Risk investment does not exactly have a guaranteed return. These are generally high-return investments in India as the returns on these investments, without a doubt, are quite high if invested wisely.

But the issue arises when the returns are not assured, and there are chances it might result in losses. The investors who pick these kinds of investments are usually the ones who are pretty savvy and are keen on the understanding of securities and more. There stands no limit to the gains in high-risk investments, but great gains come with risks too.

Here Are A Few High-Risk Investment Options

1. Direct equities

Direct Equities are also one of the best investments for long-term purposes. It is an equity share of a company, bound by legal terms which relate to company ownership.

When you buy an equity share, you get the right to be involved in the company's decision-making. But equities do also hold a high hand when it comes to risk.

2. Equity mutual funds

Equity Mutual Funds are funds that will primarily invest in stocks. You can invest your money in these stocks through SIP, little by little, or in a lump sum amount.

It suits savvy investors who are experts in the market. As you know, it is quite high when it comes to the risk involved. Your profits can be immense, but so should your risk appetite.

3. Forex trading/foreign exchange

FOREX, or Foreign Exchange, may be defined as a network of buyers and sellers who exchange currencies at an agreed-upon price. Hence, Foreign currency trading is the process through which people, businesses, and central banks exchange one currency for another.

4. Hedge funds

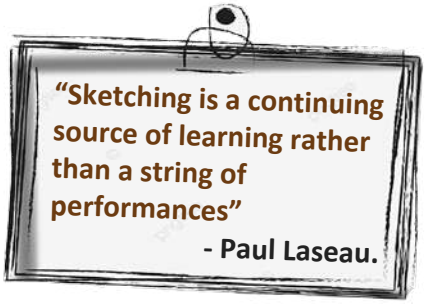
In the Securities and Exchange Board of India's (SEBI's) words, "Hedge Funds, including fund of funds, are unregistered private investment partnerships, funds, or pools that may invest and trade in many different markets, strategies, and instruments (including securities, non-securities, and derivatives) and are not subject to the same regulatory requirements as mutual funds."

Note - Although these instruments fall under High Risk, they yield high returns as well. Investors should access their risk factors before investing and conduct due diligence.

Conclusion -

You can achieve financial stability by only saving, but is that really sufficient? What if you begin saving for retirement later, which means you won't be able to cover all of the costs by saving alone.Investments are therefore always a wise choice, and this article will assist you in selecting from among the best investment plans available in India. Additionally, you always have the option to select between Low-Risk, Medium-Risk, and High-Risk investment options.

Art of charcoal painting – My passion beyond ophthalmology

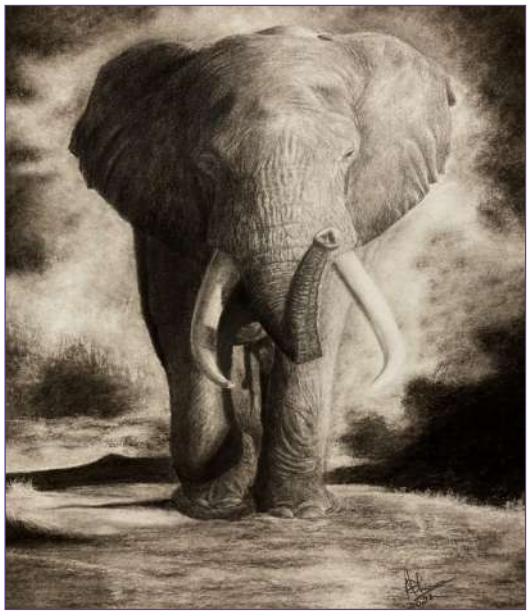


- **Dr. Ashutosh R. Boloor**
Consultant Ophthalmologist,
SDM eye hospital, Mangalore

Pencil sketching (graphite) is the best way to start for a beginner which is typically suited for smaller drawings and detailing.

Basic materials required for pencil sketches are different shades of pencils and the type of paper. As a beginner, you would basically require at the most,4 shades of pencils. HB, 2B, 6B & 9B.

The advanced professional pencil set ranges from 9H-H, F, HB-9B. where the 9H range are hard and light and gets softer towards the H and H (hard and light) to 9B (softest and the darkest). While starting a sketch the outline of the sketch using the F or the H pencil works well on smooth paper that does not leave a lot of graphite on the paper while you erase, but it has a very limited tone/shade capability. The use of pencil shades between 2B-9B requires a lot of knowledge with respect to the shades and tones of the photograph/sketch that you are sketching. Ch oosing a paper is very important in terms of its roughness & thickness. The smoother papers are good for detailed art work (ones I prefer). The graphite sticks to the paper easily and can be easily erased on this paper. Canson Biggie or strathmore 200 are good and economical choices. If you want your sketches to last longer choose acid free sketch paper & heavier weight (thickness) at least 125 gsm or more. Once you get a hang of graphite sketching you can explore different texture of paper based on the type of sketch.



There are 4 main shading techniques.

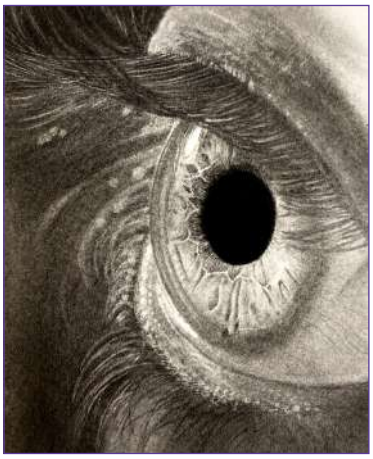
1. **Fine parallel strokes (fabric, hair, backgrounds etc.)**
2. **Cross hatching (fabric, backgrounds)**
3. **Fine circular motion.**
   (Finer detailing while drawing the eye & around it)
4. **Smooth strokes.**

The most convenient technique to start off, after getting the outline either by grid or free hand drawing is to start off from the top of the paper and work towards the bottom. Use a glossy hard paper between your hand and the art paper when you sketch to prevent the graphite from transferring to your hand. This would cause uneven patches on the art paper due to the oil from your skin. Initially I used to use my finger to blend the shades, then gradually started using cotton tipped buds, then progressed to paper blending stumps. I highly recommend using blending stumps of various thicknesses. Use of multiple stumps, from fine to blunt and shade the sketch from the lighter contrast areas to the darker areas. Judging the tone comes with practice. Every sketch is a learning experience.

Tips for beginners is to start off with a regular drawing book that your kid uses in school, once you get a hang of the strokes, pressure to be used & the blending technique you can upgrade to the different types of paper.

I have made use of technology in my art, I usually get a high quality HD photographs from the net, and then zoom into the photo and take screenshots of the finer details and try to incorporate the finest details into my sketch.My journey to charcoal sketch started off with a

pencil sketch of Sharbat Gula " Afghan girl " from the cover of the National Geographic picture shot by Mr. Steve McCurry which took nearly 20 Hours to complete. It was a daunting task as I had to get the intensity of her gaze looking at the camera.



Being a self-trained artist charcoal sketching for me was an uncharted territory. I assumed it to be more complex as it was a totally different medium. It has a powdery residue which requires paper that is more textured. The paper used here are large toned sheets of paper unlike the ones used in pencil sketches. Brevillier's Cretacolor charcoal drawing set is the one I use & Strathmore 400 series drawing paper. it was faster to draw and had a short learning curve. The downside to it is that it gets a bit messy and I couldn't draw finer details. But I would say it was still easier to produce better looking and faster sketches with charcoal than graphite.

You require 7 tools to draw, they are initially expensive, but would last a long time.

1. **Vine charcoal sticks**
2. **Alphacolor soft square pastels**
3. **Kneeded rubber eraser**
4. **Mono Zero pen style eraser**
5. **Charcoal pencil. Black & White Soft, medium & hard (soft being darker)**
6. **Blending Stumps**
7. **Strathmore 400 Series drawing sheets.**

Start off the sketch by making an outline with graphite pencil. Then, most of the charcoal sketch is done with Vine charcoal sticks as it's easily erasable. Alpha color soft charcoal is smooth and blends easily. I use a kneaded rubber eraser (which is a special eraser, it has a like putty like consistency and can be easily pulled into shapes and is easy to dab on the paper) The mono Zero pen style eraser is important in giving highlights. Alternatively, I use white charcoal pencil to give highlights and accents.

Tips that I would like to give a beginner are to use an A3 size paper and use a subject that doesn't have too much contrast and detailing. Once you get a hang of the medium you can experiment with more complex subjects.

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