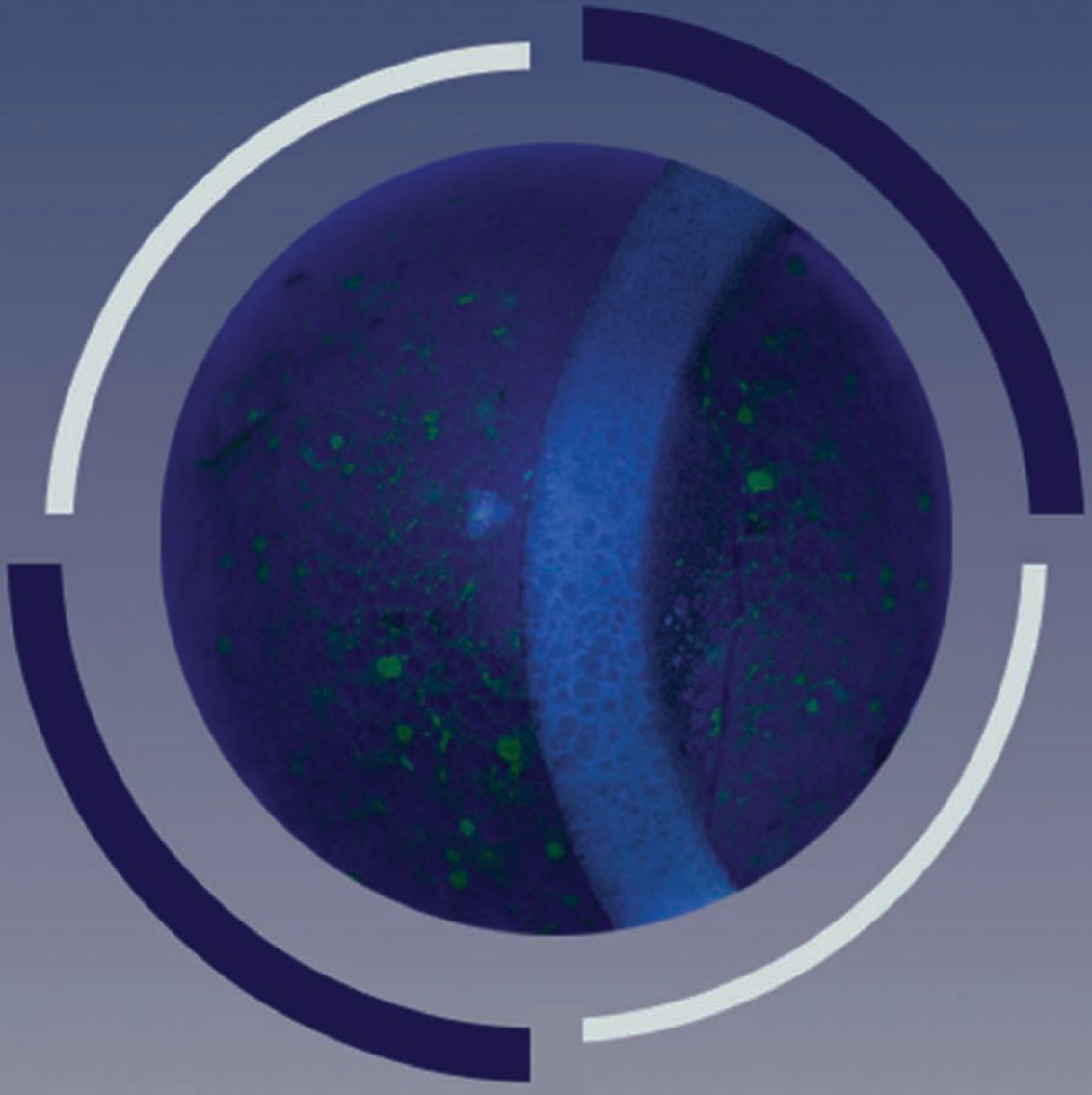
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Highlights:

Role of clinician scientists: Uncovering novel infectious uveitis in India

In vivo confocal microscopy of corneal nerves in systemic disease- A systematic review

Death on the surgical table: Medicolegal implications for doctors

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Straatsma Syndrome: An unusual cause of refractory amblyopia

KJO Videos: Double capsulorrhexis in intumescent cataracts

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Live continuing medical education programs in the era of virtual learning: Strategies for success

"Tell me and I forget, teach me and I remember, involve me and I learn" Benjamin Franklin

Continuing Medical Education (CME) programs play a crucial role in keeping ophthalmologists updated on the latest advancements in their field. However, the rise of virtual learning platforms has presented both challenges and opportunities for organizing impactful live CME programs. Currently, our state features more than one major CME program on almost all Sundays. Despite this surplus of supply, delegate enthusiasm and attendance are widely perceived to be dwindling, resulting in a sense of disenchantment for the organizing teams involved. This has raised concerns among members of the KSOS regarding the relevance and future of "real" CMEs in the present era which have been voiced in many official fora recently. Hence, the time seems ripe for review, reflection, and redemptive action if needed. This reflective essay aims to explore strategies to craft relevant and impactful live CME programs for ophthalmologists in the state of Kerala.

ARE LIVE CME PROGRAMS RELEVANT IN THE PRESENT ERA?

While virtual learning offers flexibility, accessibility, and positive learning outcomes, research on perceptive feedback from physicians point to lower learner satisfaction in online CMEs.[1] In comparison, live CME programs offer certain distinct advantages:

- **Enhance interaction and engagement**: Real-time interaction with faculty, live demonstrations, and hands on training are particularly valuable in a skill intense specialty like ophthalmology.
- **Facilitate networking and social learning:** Face-to-face networking amongst peers foster collaboration and knowledge exchange beyond the program. This is a great opportunity especially for ophthalmologists in geographically remote locations.
- **Ensure committed learning time:** A dedicated time slot and the immersive environment of a live CME program encourages focused, committed learning, whereas beneath the seeming convenience of virtual self-paced learning modules lies the unseen peril of defocus and distractions. This aspect may be more relevant for female learners, in the context of domestic expectations of multitasking often distracting them from a fully invested learning experience while attending a virtual CME from home.[2]
- **Enable learning from nonverbal cues**: Ability to read body language, facial expressions, and voice modulations enhance the quality of interactions.
- **Offer possibility of real time feedback**: Immediate clarification of doubts and real-time feedback can help facilitators modify live programs on the go.
- **Provide Opportunity for Industry exposure**: Direct access to product demonstrations, innovations, and company personnel helps professional updating and networking.
- **Offer more certification and credits**: In-person programs generally offer more credits, depending on the organization or accrediting body, thus attracting delegates who need them.
- **Improves Learning retention**: Live programs have been shown to have improved knowledge retention over time.

Hence, the case for live CMEs seems very much alive even today, as they do offer certain enduring advantages over virtual learning.

STRATEGIES TO CRAFT SUCCESSFUL LIVE CME PROGRAMS: A STEP WISE APPROACH

The strategies must leverage the abovementioned advantages at every step of planning and implementation of a live CME. Hybrid or blended models incorporating appropriate virtual elements in a real program is also a promising option. Let us look at the best practices to adopt in each step of organization of a CME.

1. Defining the target audience and doing needs assessment[3]

Planning should start early by identifying a target audience who may be comprehensive ophthalmologists/subspecialists/clinical researchers/young ophthalmologists/or any other. Whoever it may be, the organizers should not fall prey to the paternalistic "Big brother" attitude[3] of "We know what is best for you." Instead, the needs of the target audience should be sought and learning gaps identified in a truly democratic manner using audit tools/surveys/focus groups/informal one

to one feedback. This also helps to get an insight into their preferences with respect to theme, topics, formats, and optimal timings for the program.

2. Selecting a format: CME vs workshop vs update?

CME courses aim to offer broad, credit-bearing education; workshops are intended to provide targeted skill-building; and update courses deliver the latest clinical knowledge. Of these, the best fit format that matches the goal of the CME and preferences of the target group may be selected. With some extended original thinking, diverse elements of all the three may be skillfully connected to create a very engaging CME.

3. Choosing the right faculty

Select renowned experts in the field who are also engaging presenters and communicators, open to try innovative pedagogical strategies as per the requirements of the CME. A mix of established doyens and rising young stars in the field would be ideal. Repetition of topics and power point presentations by the same faculty across multiple CMEs will result in scientific programs sans power or point, and hence, the trend should be strongly discouraged.

4. Crafting an impactful scientific program

- Incorporating interactive, multisensory, and applied formats like round table interactives, workshops and skill hubs are immensely more effective than passive lectures.[4] Elements like polls, quizzes, and breakout sessions can maintain delegate engagement throughout the program.
- Blended learning models: Hybrid models incorporating virtual breakout rooms for focused discussions and e-learning modules to complement live sessions may be tried as and when necessary. Interactive exercises on user-friendly virtual platforms that are accessible across various devices may be tried if robust internet connectivity can be ensured.
- Creative learning models seamlessly blending diverse pedagogy in a sequential manner can be very refreshing. Let me explain this with an example from experience of how we used sequential blended teaching-learning strategies to advantage in a recent live CME. The delegates were primed with pre-CME learning material on the topic which was shared to them a week in advance. During the live session, the faculty took the topic forward first through power points, followed by hands on demo of the clinical tests, tool kits, and other practical aspects. Finally, real-world exposure was provided using video shows of manufacturing processes in industrial unit or faculty guided tour to real clinical setting, as was relevant to the topic concerned. The structured, blended hybrid learning experience was reported to be highly useful and engaging by many delegates.

5. Preparation and Provision of preprogram materials

Access to precourse learning modules enhance understanding during the live session of selected topics as appropriate.

6. Ensuring visibility, attracting delegates

- Utilize a multipronged marketing approach. Leverage social media platforms and professional networking sites for targeted visibility.
- Partner with ophthalmic associations, societies, and multiple hospitals to reach a wider audience.
- Early Bird Discounts and Incentives: Offer early bird registration discounts to encourage early commitment.
- Try for CME credits: Accreditation by relevant bodies like the medical council is a mark of quality that can attract ophthalmologists seeking to fulfil their CME credit requirements.

QUALITY ASSESSMENT AND FEEDBACK: WHAT DEFINES SUCCESS?

The currently popular, superfluous practice of assessing CMEs by the number of delegates alone has to be done with. Instead, we need to create technology-driven logistic systems capable of employing a combination of tools to comprehensively evaluate the impact of CME programs on improving clinical knowledge, changing physician behavior, and ultimately enhancing patient outcomes. Delegates must cooperate whole heartedly if such efforts are to bear fruit.

- Real-time feedback during the program may be collected using google forms, printed feedback forms, short break out sessions, etc., Knowing the group dynamics and specific issues can help facilitators make real-time course corrections to improve outcomes.[5] In every CME, a dedicated time can be kept aside for feedback and delegates must make it a point to use it proactively.
- Immediate outcome assessments: OSCE stations and posttests are tools used for assessment of immediate learning outcomes in medical education programs.
- Long-term outcome assessments: Automated postactivity outcome surveys, projects allotted to participants, and longitudinal tracking of individual learner journeys are methods to assess long-term success in terms of application of knowledge gained, the impact on patient care, and any changes in clinical practice.

THE WAY FORWARD

The future definitely belongs to collaboration, not competition. So why not think of "Group CMEs" where

multiple institutions can collaborate to host a single annual flagship academic event? Pooling of resources and manpower can help overcome organizational limitations, make the scientific program more robust, increase program reach, and delegate engagement. It can also address the "problem of plenty" that currently seems to plague the ophthalmic CME scene in our state, causing concern to many of our own members. The primary challenge here may surely be one of concern regarding compromise of individual branding. In this context, an encouraging example of a hugely successful collaborative educational initiative in Kerala would be the KSOS President's project of simulation-based cataract surgery training. It was one in which all the three collaborating organizations enjoyed equal brand exposure too. Similarly, if done in a spirit of true collaboration, all the stake holders involved have much to gain out of a "Group CME model." Hence, it is a promising organizational concept worth exploring further in our state.

CONCLUSION

Even in the era of virtual learning, live CME programs remain a valuable tool for professional development in ophthalmology. By understanding the evolving learning landscape and incorporating innovative strategies, one can organize impactful live CME programs that cater to the needs of the target audience, promote active learning and engagement, and ultimately achieve true success by bringing about a positive change in ophthalmic practice, education or research.

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Role of clinician scientists: Uncovering novel infectious uveitis in India

Uveitis comprises diseases of diverse etiologies, including infectious and noninfectious causes. The frequencies of these specific causes vary depending on the population studied and the geographical areas of these patient populations. The tropical countries bear a large disease burden primarily due to the high prevalence of several infectious diseases.[1] At Aravind, we encountered two epidemic outbreaks of unknown infectious uveitis and one idiopathic endemic infectious uveitis, and we were fortunate to resolve the etiology. The three novel etiologies include:

- **Leptospirosis**: Leptospirosis is a waterborne spirochetal systemic illness spread by animal urine. Rats, mice, cows, sheep, and dogs are important primary hosts. When human gets infected, they develop fever, joint pain, myalgia, muscle tenderness, and severe headache, with or without jaundice.[2] After a latent period, these patients develop nongranulomatous panuveitis. Pathognomonic clinical signs include hypopyon, vitreous membranous opacities, disc edema, and retinal vasculitis. This is a common type of uveitis seen among lower economic rural agricultural workers in tropical countries.[3,4]
- **West Nile Virus Infection**: West Nile virus (WNV) is a mosquito-borne neuroinvasive flavivirus that can infect humans, birds, mosquitoes, horses, and other mammals.[5] This viral infection is emerging globally and causes fever, joint pain, and subsequently retinitis and neuroretinitis.[6] Aravind's publication is the first Indian report to elucidate its unique ocular presentation.
- **Trematode Eye Disease in Children**: South Indian children with granulomatous anterior uveitis described a strong temporal association between the eye disease and bathing in regional ponds.[7,8] Recently, our histopathological study and molecular diagnostics identified the cause as a flatworm or trematode.[9] For over four decades, these granulomas were misdiagnosed as tubercular etiology, leading to unnecessary antitubercular treatments. This research has facilitated appropriate management of this parasitic disease.

OUTBREAK OF POST FEBRILE UVEITIS IN A FLOODED CITY

In 1993, a South Indian city, Madurai, experienced unusually heavy rainfall and flooding. Following this, residents suffered from an epidemic outbreak of febrile illness. They



were initially treated as patients of seasonal fever by primary care physicians. Subsequently, many of these patients presented at Aravind Eye Hospital with visual impairment in one or both eyes. After extensive history-taking and demographic data collection on systemic illnesses, it was noted that most patients were from the flooded parts of Madurai and had experienced fever for 1 to 2 weeks before ocular symptoms developed. Many reported severe fatigue, muscle tenderness, headache, and joint pain associated with fever. Some also had jaundice. Ocular examination revealed nongranulomatous panuveitis with hypopyon, retinal vasculitis, membranous vitreous opacities, and disc hyperemia [Figures 1-3]. What was particularly perplexing was the daily influx of a significant number of new patients with very similar clinical presentations. Over 3 months, Aravind Eye Hospital's uveitis service attended to approximately seventy-three such patients. Such numbers necessitated a search for a cause.

UNCOVERING THE CAUSE OF IDIOPATHIC UVEITIS

Extensive literature review on uveitis yielded no previous descriptions of this unusual clinical picture. Thus, investigations into endemic infectious diseases of Madurai involved consultation with several experts, including private practitioners, Government medical college physicians, municipal medical officers, and the Faculty of Social and Preventive Medicine at Madurai Medical College. Surprisingly, there was no pertinent information available. Subsequent consultations with Dr. Chandra Sekar, PhD, a microbiologist at Madurai Medical College, suggested a possible diagnosis of leptospirosis. Further collaboration with scientists from Madurai Kamaraj University, particularly Dr. Suresh Govindan,

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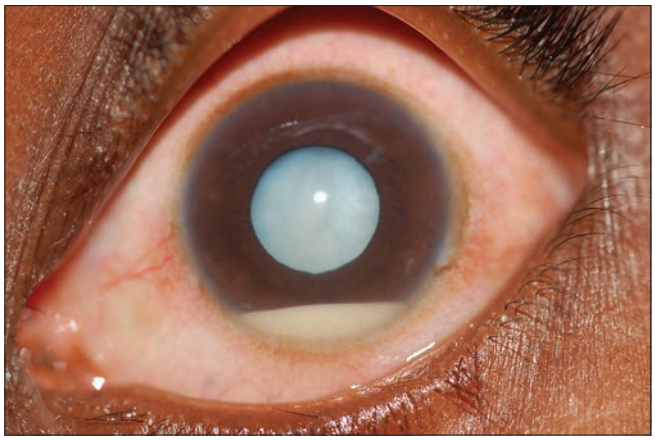


Figure 1: Hypopyon and pearly white cataract in leptospiral uveitis

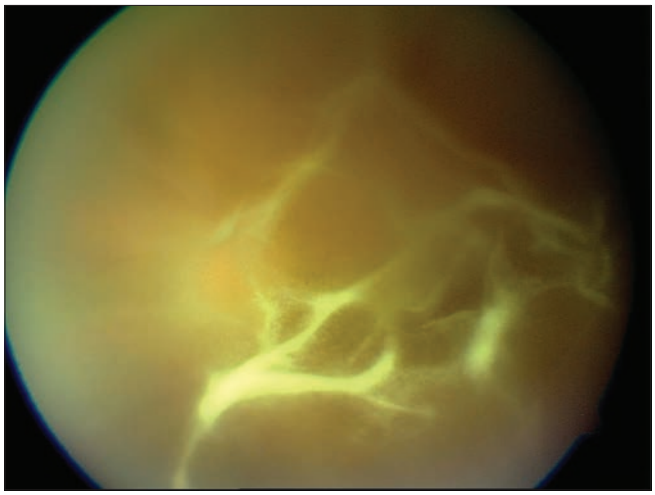


Figure 2: Disc hyperaemia and vitreous inflammatory reaction with freely floating veil like vitreous membranes in leptospiral uveitis



Figure 3: Retinal vasculitis in leptospiral uveitis

PhD, we came to know that there is a veterinary surgeon, Prof. Ratnam, at Tamil Nadu Veterinary College, Chennai. He had done PhD in veterinary leptospirosis and had an extensive experience with leptospirosis in animals.

A new dawn

In 1993–94, resources were limited. Without Wikipedia, Google, or PubMed and with few books on rare diseases in the medical college library, accessing information was challenging. Communication relied on landline phones in the form of "trunk calls," but it is possible only if the person has a land line connection at home! It was a great challenge to obtain Prof. Ratnam's expertise. However, when we finally approached him, to our surprise, he generously shared his published manual on leptospirosis, inspiring our collaboration. Dawn was breaking over the horizon! Initial serum samples, along with age-matched controls, were taken in person by the author to Prof. Ratnam for microagglutination tests to Chennai. All the serum samples of patients and controls were tested by micro agglutination test (MAT), the Gold standard test at that point of time. MAT confirmed the leptospiral etiology with significantly high positive titers in patient samples compared to controls. This breakthrough finding was published in the Indian Journal of Medical Research in 1996.[10]

CONFIRMATION AND INTERNATIONAL COLLABORATION

The next mandatory assignment was to confirm the results obtained from the regional laboratory at Chennai by cross referencing it with a World reference laboratory. Although leptospirosis is rare in developed countries, they had reference laboratories. The Center for Disease Control (CDC) in Atlanta, USA, Royal Tropical Institute, the Netherlands, and Monash University at Australia were willing to help us. Serological confirmation at all these laboratories confirmed the diagnosis of leptospiral etiology. We characterized the clinical manifestations of leptospiral uveitis, highlighting common signs such as hypopyon, hyperemic disc, retinal vasculitis, and vitreous membranes. This part of the work resulted in our first Inter National Publication in American Journal of Ophthalmology and received one of the highest citations among all our publications[3] (183 citations till now). This collaboration led to subsequent studies on cataract progression and absorption in leptospiral uveitis patients, published in the British Journal of Ophthalmology.[11]

ESTABLISHMENT OF LEPTOSPIROSIS LABORATORY

Mainland India lacked a national reference laboratory for leptospirosis. The Indian National Reference laboratory for leptospirosis is based in the Andaman Islands.[12] Establishing a regional leptospirosis laboratory in Madurai posed significant challenges. Hence, even if doctors suspected the disease, they were unable to access the service of Andaman laboratory. In addition, rapid commercial test kits were neither very specific nor sensitive.

With an aim to establish a regional laboratory at Madurai, we approached Dr. Terpstra and Dr Rudy Hartskeerl, Head, Leptospirosis Reference Centre, Royal Tropical Institute, the Netherlands, and they were much interested to give their time and expertise. Dr Rudy Hartskeerl trained the author on the microagglutination test in his laboratory in 1998. In 1999, a leptospirosis laboratory was started at Aravind Eye Hospital with the help of WOTRO Science for Global Development program, the Netherlands, the Royal Tropical Institute, the Netherlands, and Aravind Medical Research Foundation. The laboratory maintained 51 serovars. The microagglutination test was conducted every week.

This lab was serving whole of Tamil Nadu receiving blood samples from physicians as well as from ophthalmologists. Out of 31 districts, 18 districts of Tamil Nadu were using the facilities of the laboratory for the diagnosis and 22,300 blood samples have been tested in this last 15 years.

ADVANCEMENTS IN LEPTOSPIROSIS RESEARCH

Following successful clinical research on leptospiral uveitis, Aravind conducted epidemiological, basic, and diagnostic studies.[13-22] Under the guidance of Prof. VR. Muthukaruppan, Director of Research at Aravind Medical Research Foundation, experiments explored the value of culture and serology in ophthalmic complications of leptospirosis. A pilot study established leptospiral etiology of uveitis, published in the Journal of Medical Microbiology with a cover picture. Further research suggested a role for serovar-specific lipopolysaccharides in aqueous humor, indicating leptospiral uveitis as a distinct entity from other forms of uveitis.[14] The study was on nature of infiltrating cells and the profile of cytokines which was published in the prestigious international journal IOVS.[15]

In collaboration with the Hyderabad Central University and University of Kentucky, various antigens were studied for their antigenicity, and the findings were published in both national and international journals.[16,17] In addition, commercially available diagnostic kits were tested for its usefulness in clinical practice.[18] Diagnostic research led to the development of a clinical decision rule (CDR), using logistic regression to analyse each clinical sign's diagnostic predictive value.[19] CDR validation was subsequently published.[20]

EPIDEMIOLOGICAL AND SOCIAL RESEARCH IN LEPTOSPIROSIS

Despite reporting seropositivity in uveitis patients, there was limited literature from veterinary surgeons or primary care physicians in Madurai. In order to find out the veterinary sero prevalence and to isolate leptospires from large and small animals, we worked with veterinary surgeons from the Netherlands. Field rats and bandicoots were collected from villages around Madurai and brought back to Aravind eye hospital for dissection. Urine and kidney samples were cultured. Serum samples were collected from cattle and goat from urban centers as well as from the paddy fields around Madurai district. The study concluded that the field rats were a major infectious source of leptospirosis in and around Madurai.[21,22]

Subsequently, we did social science research to understand Knowledge, Attitude, and Practice Toward Leptospirosis among rural, urban population, and in under graduate and post graduate medical students.[23,24] Several other clinical, sero prevalence studies were published in recent years.[4,25-28] In conclusion to increase awareness, several book chapters on leptospiral uveitis have been written from Aravind in National and international uveitis books.

II Next febrile disease arrives at Madurai

In 2010, Aravind received nearly 200 patients with fever, joint pain, and vision impairment. Several initial tests for infectious diseases like typhoid, leptospirosis, tuberculosis, dengu, and chikungunya yielded negative results locally. Further tests at Unité de Recherche sur les Maladies Infectieuses et Tropicales Emergentes (URMITE) in France revealed absence of Rickettsia or Bartonella. Additional virological work up was needed. We approached Dr. Manmohan Parida, PhD, Division of Virology, Defense Research and Development Establishment (DRDE). The samples were sent to DRDE, Gwalior. Serology for chikungunya and dengue was repeated by lateral flow assay, with the kit received from Standard Diagnostics, Korea. The tests results came negative. We felt we have landed on a dead end again.

Further DRDE in-house IgM ELISA and antigen-capture ELISA were performed for WNV. To our surprise, serology was positive for WNV. West Nile virus was never suspected by us, as the clinical pictures described in ocular WNV in the literature was chorioretinitis and our patients showed retinal cotton wool spots and neuroretinitis [Figure 4]. Moreover, serology is not the final test as it can be a false positive due to cross reacting antigens.

More evidence still needed to pinpoint the cause

Hence, we needed further evidence to confirm the etiology. Serum/plasma samples were again tested by real-time polymerase chain reaction (RT PCR), and the PCR product was sent for nucleotide sequencing. The BLAST analysis of RT PCR amplicon confirmed West Nile Virus genogroup I lineage.

Aravind is fortunate again

This is the first Indian report on West Nile Virus retinitis in the eye, and this part of the work was published in the International Journal of Infectious Diseases, Journal of Clinical Virology and in the Journal, Ophthalmology.[29-31] Because of its unique nature of clinical presentation in India, the pictures are accepted for the cover in the Journal of Ophthalmology.[6]

Ill Children go blind – Chase the cause – Is it TB?

Numerous children from villages along the East coast of Tamil Nadu presented with granulomas in the anterior chamber of their eyes or in the subconjunctival plane. This issue persisted for 30 to 40 years, often suspected to be tubercular uveitis by ophthalmologists despite the lack of laboratory evidence supporting tuberculosis.[32] Over three decades, research was dedicated to uncover the cause of this unique eye condition. With support from the Indian Council of Medical Research, we conducted smear, culture, and polymerase chain reaction tests on these granulomas for tuberculosis, but all results returned negative. Furthermore, treatment with antitubercular medications did not control uveitis.

We had our first uveitis camp!

We needed to understand the problem from its root. A detailed plan was formulated and executed. The pivotal moment came with our first uveitis camp to Sellananthal village from where we had significant number of patients. On examination, 41 children were found to have the same granulomatous eye disease [Figures 5 and 6]. Extensive interviews with their families revealed a common history: the children developed itching and mass lesions in their eyes after bathing in the village pond, with some children experiencing vision loss.

Initially, water samples from the village pond were sent to the King Institute in Chennai for analysis, but no relevant information on the cause was obtained. Subsequent microscopic examination of water samples in our laboratory demonstrated significant contamination, yet the specific cause remained elusive. Eventually, in our subsequent camps, the affected children were brought to the base hospital, where excision biopsies of their granulomas were conducted for histopathological studies.

Focus shifts to a parasite!

Collaborating with Prof. Narsing A. Rao of Los Angeles, USA, and Prof. Fritche A. Thomas, USA, we conducted histopathological analysis, which suggested a potential parasitic cause, specifically implicating a trematode. Trematodes, or flatworms, are known to be transmitted by snails. However, the histopathological examination did not definitively identify the exact parasite.[7,8]

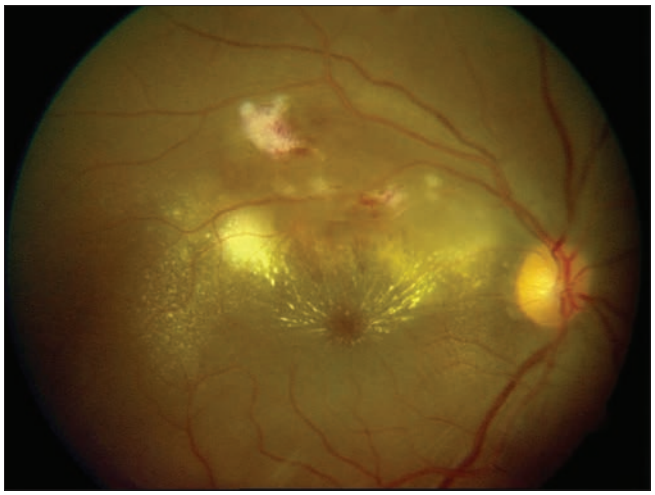


Figure 4: Retinitis with superficial hemorrhage and macular star in a patient with West Nile Virus infection

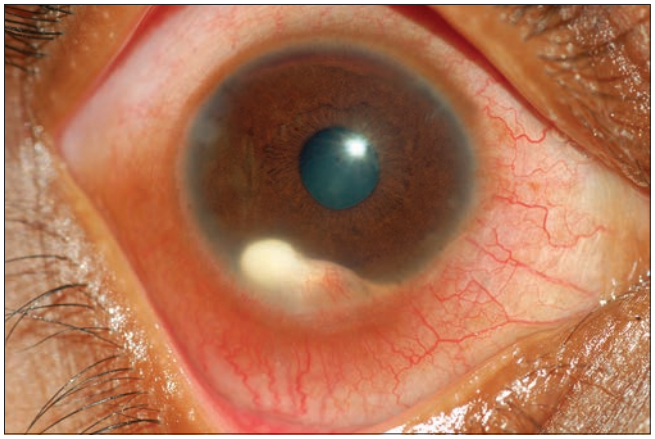


Figure 5: Anterior chamber trematode granuloma in a child

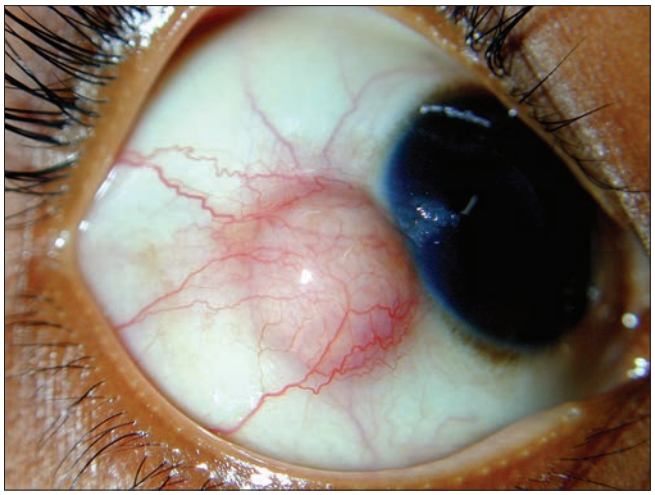


Figure 6: Subconjunctival trematode granuloma

In pursuit of further clues, our team visited numerous villages and collected multiple snail specimens for identification. These snails were sent to the Zoological Survey of India in Kolkata for expert analysis. In 2000, through discussions and

training with parasitologists at Sun Yat University in China, we learned about the isolation of trematodes from snails. Despite the abundance of snails and flatworms, pinpointing the specific trematode responsible for the disease seemed increasingly challenging.

Dead snails travel to Meghalaya

At this juncture, molecular diagnostics emerged as a promising avenue. We sought collaboration with laboratories specializing in molecular diagnostics for this purpose. Professor R. George Michael from North Eastern Hill University (NEHU), Meghalaya, introduced us to Professor Veena Tandon, who was actively engaged in research on parasite biodiversity, molecular taxonomy, and phylogeny at NEHU. Following extensive discussions, we decided to send our specimens from Tamil Nadu to Meghalaya.

Under Professor Tandon's expertise, we were able to unravel the mystery surrounding the eye condition that had plagued our children for nearly four decades. Molecular techniques including Real-Time PCR, Syber green Assay, Bidirectional sequencing, and BLAST analysis conclusively identified the causative agent as Procerovum varium, a trematode of the family Heterophyidae. This ground breaking research was subsequently published in the esteemed Journal, " Archives of Ophthalmology: and in Emerging Infectious Disease.[9,33]

This discovery was pivotal in guiding doctors away from unnecessary antituberculosis treatments, which could have been detrimental to the children. Lalan Kumar Arya, who assisted in the initial collaboration, has now completed his PhD focusing on the immunopathogenesis of subconjunctival and anterior chamber granulomatous uveitis in children of South India.[33,34]

CONCLUSION

Uveitis in developing world often presents causes rarely encountered in developed nations.[1] However, research on Paediatric Trematode granuloma has global implication as the disease is seen in other countries such as Sri Lanka, south Asian countries, Egypt, and Brazil. Regional health research is crucial for understanding environmental and socioeconomic risk factors. In addition, regional health research allows us to understand region-specific diseases, which helps us in improving diagnostic accuracy and treatment efficacy.

Aravind Eye Care System's research efforts have successfully elucidated the etiology of three rare diseases. We acknowledge our collaborators, patients, nursing staff, administrative staff, and mentors at Aravind Eye Care System for their unwavering support.

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Review Article

In vivo confocal microscopy of corneal nerves in systemic disease- A systematic review

ABSTRACT

This review was conducted to study the pattern of changes in the morphology of corneal nerves by in vivo confocal microscopy(IVCM) in various systemic diseases and evaluate the usefulness of this examination modality in diagnosis, treatment and prognosis of various systemic diseases. Articles were searched using the following keywords 'Corneal nerves' , 'sub basal plexus' , 'confocal microscopy', 'corneal nerve fibre density' , 'corneal nerve fibre length' , 'corneal nerve branch density' , 'cross sectional study', 'prospective study', either singly or combined. Databases searched include Pubmed, Cochrane library, Embase and Science Direct. The search strategy was to include studies in which corneal nerve morphology was studied in relation to a systemic condition. 26 studies were included in this review. Changes in corneal nerve parameters were noted in systemic diseases like Diabetes Mellitus, Parkinson's disease, Migraine etc. IVCM examination of corneal nerves has great scope as a screening tool for patients prone to develop neuropathies and also in monitoring the progression in neuropathies and certain neurological conditions.

Keywords: Corneal nerves, *in vivo* confocal microscopy, systemic disease

INTRODUCTION

The cornea is a highly sensitive structure with the richest nerve supply in the human body.[1] The nerves of the cornea are arranged in 4 layers: mid stromal nerves, sub epithelial plexus, sub basal plexus and intraepithelial nerve terminals. Nerve fibres arising from the trigeminal ganglion cells, travel suprachoroidally and ultimately form the limbal plexus at the corneoscleral limbus.[2] Nerve fibers arising from the plexus radially enter the corneal stroma after losing their perineurium and myelin sheath. They run horizontally, divide into smaller branches and form the stromal nerve plexus.[3] The stromal nerves at a certain point change their course, turn 90 degrees, run into the epithelium, penetrates the Bowman's membrane, and branch further to form the sub basal plexus, located between the Bowman's membrane and epithelial basement membrane. These nerves run centripetally towards the centre of the cornea and whorl towards the inferonasal paracentral area. The sub basal plexus also gives rise to intraepithelial terminals, which either branch or end as free nerve endings in the epithelium. The sub epithelial plexus lies in the interface between the Bowman's membrane and anterior stroma.[4] Important functions of the corneal nerves include sensing chemical and mechanical stimuli, pain and sensing temperature changes.[5] 70%–90% of the corneal nerve fibers are small A3 and C nerve fibers.[6] The structure and function of corneal nerves are affected by many systemic conditions and abnormalities have been noted in a number of systemic and local conditions.[7] The development of *in vivo* confocal microscopy (IVCM) and more recently laser IVCM has provided ophthalmologists with a valuable tool to study in detail the morphology and anatomy of the corneal nerves, including the sub basal nerve plexus.[8] The sub basal nerves are seen as well defined, densely anastomosed

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structures with homogenous reflectivity and Y or H-shaped branches. Stromal nerves are seen in the anterior and mid stroma as thick and bright structures with no internal details visible. However, the sub epithelial plexus is of low contrast and is seen as sparsely distributed varicosities in the anterior stroma.[4] Nerve parameters are quantified using software to help analyze nerve parameters (eg., ACC Metrics, University of Manchester). The commonly used parameters that are analyzed include Corneal nerve fiber density (CNFD - number of fibers/mm^2), Corneal nerve fiber length (CNFL-total length of nerves (mm)/mm^2), Corneal nerve branch density (CNBD - number of branch points on the main fibers/mm^2), nerve fibre total branch density (CTBD - total number of branch points/mm^2), nerve fibre area (CNFA- total nerve fibre area in mm^2/mm^2 of cornea), nerve fiber width (CNFW- average corneal nerve fibre width in mm/mm^2 of cornea) etc.[9] IVCM examination of corneal nerves provides a useful, non invasive way to detect corneal nerve changes and to follow up on these changes easily. A number of studies have revealed corneal neural structural and functional abnormalities in the background of a number of ocular and systemic diseases. The aim of this study was to review the pattern of changes in the morphology of corneal nerves by IVCM in various systemic diseases and evaluate the usefulness of this examination in the diagnosis, treatment, and prognosis of various systemic diseases.

MATERIALS AND METHODS

Search strategy

The search strategy included the following keywords: 'Corneal nerves', 'sub basal plexus', 'confocal microscopy', 'corneal nerve fiber density', 'corneal nerve fiber length', 'corneal nerve branch density', 'cross-sectional study', 'prospective study', either singly or combined. Databases searched include Pubmed, Cochrane Library, Embase, and Science Direct. The search strategy was to include studies in which corneal nerve morphology was studied about a systemic condition.

Inclusion and exclusion criteria

Studies were included if they fulfilled the following criteria:

1. Studies involving the morphology of corneal nerves and a systemic disease
2. Studies involving human subjects only
3. Studies using IVCM
4. Studies in which English full text could be obtained.

Studies excluded were those in which corneal nerve morphology was not studied in relation to a systemic condition and those studies in which English text could not be obtained.

RESULTS

After applying the inclusion and exclusion criteria, 26 studies were included in this review. 123 studies were retrieved, out of which only 26 studies could be included in the review. Reasons for exclusion included studies in other languages, veterinary studies and studies not involving a specific systemic condition. The studies included 2355 participants, including 791 healthy controls. Of the 26 researches, 8 involved Diabetic patients, 4 researches studied the changes in corneal nerve parameters in patients with Parkinson's disease, 3 involved Migraine patients, 3 were post-COVID changes and 2 studies were regarding corneal changes in patients with Amyloidosis. There were also 3 studies showing corneal changes in polyneuropathies and 3 studies involving corneal nerve changes in miscellaneous systemic conditions. The corneal nerve parameters showed changes in many of these systemic conditions and it also served as a screening tool in many of these conditions.

DISCUSSION

There were 8 researches regarding the changes in corneal parameters in Diabetic patients. [Table 1] Statistically significant changes in corneal nerve parameters were noted in Diabetic patients, even those without clinical evidence of retinopathy or neuropathy.[10] The corneal nerve parameters that were altered include a reduction in CNFD, CNFL, and CNBD. Besides these, corneal nerve tortuosity was also found to be reduced in all types of Diabetic patients.[11] All the corneal parameters were found to be lower in Diabetic neuropathy patients, more so in those with painful neuropathy and they were found to correlate with other neural parameters like tibial and sural nerve conduction amplitude and velocity.[12-14] Another structural corneal nerve change noted in Diabetic patients was a loss of nerves at the inferior and central corneal whorl region.[15,16] The changes in corneal parameters in Diabetic subjects were found to progressively worsen over time.[15] Corneal nerve parameter changes were also noted in children with type 1 Diabetes Mellitus, which included a reduction in CNFD, CNFL, CNBD, and inferior whorl length.[17] These studies thus demonstrate the utility of IVCM examination of corneal nerves as a simple, useful, and non-invasive screening tool for predicting the development of neuropathy and can also be used to screen prediabetic or genetically predisposed individuals to predict the risk of developing clinical Diabetes. IVCM examination in Diabetic patients thus gives an insight into the general condition of the neurological structure and function of the nerves, not only in the cornea but the body in general.

Table 1: IVCM and Diabetes Mellitus

Name of author	Stydy type	Study population	Aim	Results	Conclusion
Carmichael J *et al*. *	Cross sectional	20 patients with type 1 DM, 15 healthy controls	To assess the corneal and retinal nerve fiber pattern and density in patients with Type 1 DM without an evidence of retinopathy	Statistically significant changes in both RNFL and corneal nerve fiber morphology were noted in patients with DM compared to controls	Corneal nerve fiber examination is a simple method which give us and insight into the state of nerves in Diabetic patients, even those without clinical neuropathy
Klisser J *et al*. +	Cross sectional	51 type 1 DM patients, 56 type 2 DM patients. 64 controls	To evaluate corneal nerve tortuosity in patients with type 1 and 2 DM and the relationship between tortuosity and neuropathy status	Tortuosity was significantly reduced in both types of Diabetes compared to controls and in patients with neuropathy compared to patients with no neuropathy	Loss of corneal neural tortuosity would serve a reflection of changes occurring in nerves elsewhere and corneal nerve changes serve as a marker for neuropathy.
Kalteniece A *et al*. ++	Cross sectional	113 Diabetic neuropathy patients and 38 healthy controls	To study if there is any relationship between severity of corneal nerve loss and severity of painful Diabetic neuropathy	CNFD and CNFL were were significantly lower in patients with more severe pain and the difference in CFND correlated with the severity of pain.	Confocal microscopic examination of corneal nerves could help in identifying patients with painful Diabetic neuropathy
Pacaud D *et al*. $	Cross sectional	83 children with type 1 DM and 83 healthy controls	To assess corneal nerve parameters and compare them to other motor and sensory nerve parameters in patients with type 1 DM	Corneal nerve fiber density, fiber length and branch density were lower in patients with type 1 DM compared to healthy controls. Tibial motor nerve amplitude and conduction velocity and sural sensory nerve amplitude and conduction velocity were also lower. However clinically only 3 participants had subclinical neuropathy.	Corneal nerve fiber analysis could prove to be a very useful non invasive screening method to detect sub clinical neuropathy in children with type 1 DM
Kalteniece A *et al*. !	Cross sectional	78 patients with painful Diabetic neuropathy, 62 with painless neuropathy and 30 healthy controls	To assess if IVCM can distinguish between painful and painless diabetic neuropathy and to assess if severity of corneal nerve damage is related to the severity of neuropathic pain and quality of life	All IVCM parameters like CNFD, CNBD, CNFL and IWL were lower in both groups of Diabetic neuropathy patients compared to healthy controls. CNFD, CNBD and CNFL were lower in painful neuropathy compared to painless neuropathy.	IVCM identifies greater small nerve fiber damage in patients with Diabetic neuropathy and this correlates with severity of pain and lower quality of life index
Ferdousi M *et al*. +++	Longitudinal cross sectional	30 patients with DM, 19 controls	To assess longitudinal changes in corneal nerve morphology in the central cornea and the inferior whorl region.	Over the period of follow up ranging from 1 to 8 years, significant decrease was noted in CNFL, CNBD and IWL and no change in CNFD.	IVCM can help in follow up of neuropathy in patients with DM
Ferdousi M *et al*. #	Cross sectional	51 Diabetic patients without neuropathy, 47 with mild neuropathy and 45 with moderate neuropathy. 30 age matched controls	To find out if there is a relationship between corneal nerve parameters, sural NCV, vibration and warmth perception threshold in patients with different severities of Diabetic neuropathy	All previously mentioned parameters showed increasing range of abnormalities correlating with the severity of neuropathy. There is also progressive loss of corneal nerves at the inferior and central whorl region with increasing severity of Diabetic retinopathy.	Confocal corneal microscopic study of corneal nerve patterns has comparable efficiency to NCV and sensory testing in diagnosis and stratification of Diabetic neuropathy.

Contd...

Table 1: Contd...

Name of author	Study type	Study population	Aim	Results	Conclusion
Gad H *et al*. **	Cross sectional	20 subjects, 20 controls	To assess stromal keratocyte density and nerve fiber changes in children with type 1 DM and the relationship between them	Corneal nerve fiber density, nerve fiber length, branch fiber density and inferior whorl length were lower in children with Type 1 DM compared to healthy controls.	Corneal nerve fiber morphological alterations reflect changes in nerves in the body and also highlight the fact that Diabetic neuropathy could be diagnosed earlier by studying the corneal nerves *in vivo*

The above table shows studies correlating changes in IVCM parameters and Diabetes Mellitus. *Carmichael J, Fadavi H, Tavakoli M. Neurodegeneration of the cornea and retina in patients with type 1 diabetes without clinical evidence of diabetic retinopathy. Front Endocrinol (Lausanne). 2022 Oct 5;13:790255. doi: 10.3389/fendo. 2022.790255. PMID: 36277683; PMCID: PMC9581164. + Klisser J, Tummanapalli SS, Kim J, Chiang JCB, Khou V, Issar T, Naduvilath T, Poynten AM, Markoulli M, Krishnan AV. Automated analysis of corneal nerve tortuosity in diabetes: implications for neuropathy detection. Clin Exp Optom. 2022 Jul; 105(5):487-493. doi: 10.1080/08164622.2021.1940875. Epub 2021 Jul 27. PMID: 35772934. ++ Kalteniece A, Ferdousi M, Azmi S, Khan SU, Worthington A, Marshall A, Faber CG, Lauria G, Boulton AJM, Soran H, Malik RA. Corneal nerve loss is related to the severity of painful diabetic neuropathy. Eur J Neurol. 2022 Jan; 29(1):286-294. doi: 10.1111/ene. 15129. Epub 2021 Oct 13. PMID: 34570924; PMCID: PMC9292015. $ Pacaud D, Romanchuk KG, Virtanen H, Ferdousi M, Nettel-Aguirre A, Mah JK, Tavakoli M, Zochodne DW, Malik RA. Corneal nerve and nerve conduction abnormalities in children with type 1 diabetes. Pediatr Diabetes. 2022 Dec; 23(8):1665-1673. doi: 10.1111/pedi. 13419. Epub 2022 Oct 3. PMID: 36131228. ! Kalteniece A, Ferdousi M, Azmi S, Mubita WM, Marshall A, Lauria G, Faber CG, Soran H, Malik RA. Corneal confocal microscopy detects small nerve fiber damage in patients with painful diabetic neuropathy. Sci Rep. 2020 Feb 25;10(1):3371. doi: 10.1038/s41598-020-60422-7. PMID: 32099076; PMCID: PMC7042367. +++ Ferdousi M, Kalteniece A, Petropoulos I, Azmi S, Dhage S, Marshall A, Boulton AJM, Efron N, Faber CG, Lauria G, Soran H, Malik RA. Diabetic Neuropathy Is Characterized by Progressive Corneal Nerve Fiber Loss in the Central and Inferior Whorl Regions. Invest Ophthalmol Vis Sci. 2020 Mar 9;61(3):48. doi: 10.1167/iovs. 61.3.48. PMID: 32232351; PMCID: PMC7401481. # Ferdousi M, Kalteniece A, Azmi S, Petropoulos IN, Worthington A, D'Onofrio L, Dhage S, Ponirakis G, Alam U, Marshall A, Faber CG, Lauria G, Soran H, Malik RA. Corneal confocal microscopy compared with quantitative sensory testing and nerve conduction for diagnosing and stratifying the severity of diabetic peripheral neuropathy. BMJ Open Diabetes Res Care. 2020 Dec; 8(2):e001801. doi: 10.1136/bmjdrc-2020-001801. PMID: 33355206; PMCID: PMC7754626. ** Gad H, Al-Jarrah B, Saraswathi S, Mohamed S, Kalteniece A, Petropoulos IN, Khan A, Ponirakis G, Singh P, Khodor SA, Elawad M, Almasri W, Hendaus MA, Akobeng AK, Hussain K, Malik RA. Corneal confocal microscopy identifies a reduction in corneal keratocyte density and sub-basal nerves in children with type 1 diabetes mellitus. Br J Ophthalmol. 2022 Oct; 106(10):1368-1372. doi: 10.1136/bjophthalmol-2021-319057. Epub 2021 Apr 30. PMID: 33931390

Table 2: IVCM and Parkinson's disease

Name of author	Type of study	Population	Aim	Result	Conclusion
Lim SH *et al*. *	Cross sectional prospective	64 participants, 25 controls	To assess corneal nerve fiber patterns in patients with Parkinson's disease (PD) and to assess it relation to disease progression.	Corneal nerve fiber length, density, and branch density (CNFL, CNFD, CNBD) were significantly lower in Parkinson disease patients compared to healthy volunteers. However, no change in corneal nerve parameters were noted over the 12-month period.	Morphological alterations in corneal nerves are a marker for neurodegeneration
Kass-Iliyya L *et al*. +	Cross sectional	26 patients with PD, 26 controls	To study corneal nerve fiber damage in PD, its correlation with intraepidermal nerve damage and clinical features of PD	CFND was significantly reduced, CFBD and CFNL were increased. They correlated with deep breathing heart rate variability. IENFD was significantly reduced.	Corneal nerve parameters correlated with autonomic dysfunction in PD patients. But it still remains unanswered if IVCM examination of corneal nerves could be a biomarker of subclinical PD
Che NN *et al*. ++	Cross sectional	65 PD patients, 36 controls	To study the relationship between corneal parameters and cognitive impairment in PD patients	CNFD was reduced and CBFD was increased in PD patients. CNFD was positively correlated with the Montreal cognitive assessment score but negatively with unified Parkinson disease scale.	Corneal nerve parameters are found to correlate with the severity of cognitive and motor impairment in PD patients and thus serves as a biomarker of neurodegeneration.
Che NN *et al*. $	Cross sectional	29 patients with a tremor dominant Parkinson's disease (TD) subtype, 34 patients with postural instability and gait disturbance (PIGD), and 10 had mixed subtype	To explore any relationship between the pattern of PD and the extent and pattern of corneal nerve loss	CNFD, CNBD and CNFL were lower in PIGD group compared to the TD group	IVCM analysis may have a role in differentiating between different subtypes of PD

The above table shows the IVCM findings in patients with Parkinson's disease. * Lim SH, Ferdousi M, Kalteniece A, Mahfoud ZR, Petropoulos IN, Malik RA, Kobylecki C, Silverdale M. Corneal Confocal Microscopy Identifies Parkinson's Disease with More Rapid Motor Progression. Mov Disord. 2021 Aug; 36(8):1927-1934. doi: 10.1002/mds. 28602. Epub 2021 Apr 7. PMID: 33826165. + Kass-Iliyya L, Javed S, Gosal D, Kobylecki C, Marshall A, Petropoulos IN, Ponirakis G, Tavakoli M, Ferdousi M, Chaudhuri KR, Jeziorska M, Malik RA, Silverdale MA. Small fiber neuropathy in Parkinson's disease: A clinical, pathological, and corneal confocal microscopy study. Parkinsonism Relat Disord. 2015 Dec; 21(12):1454-60. doi: 10.1016/j.parkreldis. 2015.10.019. Epub 2015 Nov 3. PMID: 26578039; PMCID: PMC4671992. ++ Che NN, Jiang QH, Ding GX, Chen SY, Zhao ZX, Li X, Malik RA, Ma JJ, Yang HQ. Corneal nerve fiber loss relates to cognitive impairment in patients with Parkinson's disease. NPJ Parkinsons Dis. 2021 Sep 9;7(1):80. doi: 10.1038/s41531-021-00225-3. PMID: 34504084; PMCID: PMC8429586. $ Che NN, Jiang QH, Chen S, Chen SY, Zhao ZX, Li X, Ma JJ, Zhang JW, Malik RA, Yang HQ. The severity of corneal nerve loss differentiates motor subtypes in patients with Parkinson's disease. Ther Adv Neurol Disord. 2023 Apr 19;16:17562864231165561. doi: 10.1177/17562864231165561. PMID: 37114067; PMCID: PMC10126700

Table 3: IVCM and Migraine

Name of author	Type of study	Population	Aim	Result	Conclusion
Guldiken YC *et al*. *	Cross sectional	60 migraine patients, 20 controls	Confocal microscopic assessment of corneal nerve fiber patterns was undertake after analyzing the pattern of migraine in the study population	Corneal nerve fiber density, branch density and length (by both manual and automated means was lower in patients with migraine and these changes were more severe in chronic migraine.	Confocal microscopic examination of corneal nerves could serve as a biomarker of neurodegeneration in patients with longstanding migraines
Kinard KI *et al*. +	Cross sectional	19 chronic migraine patients, 30 controls	To assess if there is a structural difference in the sub basal corneal nerve plexus between chronic migraine patients and controls	There was a reduction in both CNFL and CNFD in chronic migraine patients and reduction in CNFD was found to be significant.	The trigeminal system plays crucial role in the pathogenesis of migraine and this hypothesis is supported by changes in the corneal nerve fiber pattern
Shetty R *et al*. ++	Cross sectional	36 patients with migraine + photophobia, 24 with migraine without photophobia and 24 controls were included in the study	To study the changes in the corneal sub basal plexus in migraine patients with/without photophobia	There was a significant reduction in CNFL, CBFD, total branch density, nerve branch density and fiber area in migraine patients with photophobia compared to migraine patient without photophobia	Corneal nerve pattern examination could serve as a potential marker for ocular symptoms of chronic migraine and this further strengthens the hypothesis regarding the role of the trigeminal nerve in the pathogenesis of Migraine

The above table shows the relationship between IVCM parameters and Migraine patients. * Guldiken YC, Petropoulos IN, Malik A, Malik RA, Yüksel R, Budak F, Selekler HM. Corneal confocal microscopy identifies corneal nerve fiber loss in patients with migraine. Cephalalgia. 2023 May; 43(5):3331024231170810. doi: 10.1177/03331024231170810. PMID: 37177828. + Kinard KI, Smith AG, Singleton JR, Lessard MK, Katz BJ, Warner JE, Crum AV, Mifflin MD, Brennan KC, Digre KB. Chronic migraine is associated with reduced corneal nerve fiber density and symptoms of dry eye. Headache. 2015 Apr; 55(4):543-9. doi: 10.1111/head. 12547. Epub 2015 Mar 31. PMID: 25828778; PMCID: PMC4887261. ++ Shetty R, Deshmukh R, Shroff R, Dedhiya C, Jayadev C. Subbasal Nerve Plexus Changes in Chronic Migraine. Cornea. 2018 Jan; 37(1):72-75. doi: 10.1097/ICO.0000000000001403. PMID: 28990996

Table 4: IVCM AND COVID-19

Name of author	Type of study	Population	Aim	Result	Conclusion
Barros A *et al*. *	Observational retrospective study	23 subjects, 46 controls	To assess the relationship between SARS- CoV2 infection and corneal small fiber neuropathy	Post COVID patient showed a significant reduction in corneal nerve fiber length and density in the 35–55-year age group as compared to healthy controls.	Damage to the corneal nerves post COVID is probably one of the factors involved in the pathogenesis of post COVID dry eye disease and a pointer to associated or forthcoming peripheral neuropathies
Bitirgen G *et al*. +	Cross sectional comparative study	40 COVID-19 recovered patients and 30 controls.	To assess sub basal nerve fiber morphology and inflammatory cell infiltration in patients with and without long COVID	Patients with neurological symptoms 4 weeks after COVID-19 infection had lower CNFD, CNFL and CNBD compared to patients without neurological symptoms and controls. Dendritic cell counts were raised in all post COVID patients	This examination could be used as an objective method to identify long COVID
Midena E *et al*. ++	Cross sectional study	142 COVID-19 patients and 47 controls	To study the involvement of small corneal peripheral nerve fibers in recovered COVID-19 patients	Corneal nerve branch density and fiber tortuosity was increased, whereas there was a reduction in corneal nerve fiber area and number of beadings.	COVID-19 may induce peripheral neuropathy in small nerves in the body.

The table demonstrates the corneal parameters in post COVID patients. * Barros A, Queiruga-Piñeiro J, Lozano-Sanroma J, Alcalde I, Gallar J, Fernández-Vega Cueto L, Alfonso JF, Quirós LM, Merayo-Lloves J. Small fiber neuropathy in the cornea of Covid-19 patients associated with the generation of ocular surface disease. Ocul Surf. 2022 Jan; 23:40-48. doi: 10.1016/j.jtos. 2021.10.010. Epub 2021 Nov 12. PMID: 34781021; PMCID: PMC8588585. + Bitirgen G, Korkmaz C, Zamani A, Ozkagnici A, Zengin N, Ponirakis G, Malik RA. Corneal confocal microscopy identifies corneal nerve fiber loss and increased dendritic cells in patients with long COVID. Br J Ophthalmol. 2022 Dec; 106(12):1635-1641. doi: 10.1136/bjophthalmol-2021-319450. Epub 2021 Jul 26. PMID: 34312122; PMCID: PMC8359871. ++ Midena E, Cosmo E, Cattelan AM, Briani C, Leoni D, Capizzi A, Tabacchi V, Parrozzani R, Midena G, Frizziero L. Small Fiber Peripheral Alterations Following COVID-19 Detected by Corneal Confocal Microscopy. J Pers Med. 2022 Apr 1;12(4):563. doi: 10.3390/jpm12040563. PMID: 35455679; PMCID: PMC9030195

Parkinson's disease is a rapidly growing neurodegenerative condition, generally recognized as a syndrome with a wide range of aetiologies and clinical manifestations.[18] There were 4 studies regarding corneal nerve changes in Parkinson's disease included in this review. [Table 2] Corneal nerve fiber density was found to be reduced in all these studies. Universal reduction in corneal parameters was noted in a study, which showed no worsening over the 12-month study period.[19] Corneal parameters were noted to correlate with autonomic dysfunction in these patients and to the severity

Table 5: IVCM and amyloidosis

Name of author	Type of study	Population	Aim	Result	Conclusion
Avetisov SE *et al*. *	Cross sectional study	16 patients with AL-amyloidosis (light chain amyloidosis) and 14 patients with TTR amyloidosis (transthyretrin amyloidosis)	To assess the state of corneal nerve fibers in patients with amyloidosis bt confocal microscopy	Increased tortuosity of the corneal nerve fibers was noted in patients with Amyloidosis and the changes were more pronounced in TTR amyloidosis	Confocal microscopic microscopic examination of corneal nerve fibers is a simple method to assess systemic amyloidosis qualitatively and quantitatively
Thimm A *et al*. +	Cross sectional	21 newly diagnosed AL amyloidosis cases and 21 healthy controls	To assess changes in the corneal nerve fibers in patients with newly diagnosed AL amyloidosis	There was a significant reduction in CNFD and CNFL.	IVCM examination detects early small nerve fiber damage earlier than Nerve conduction studies and allows early small nerve fiber damage non-invasively.

Relationship between IVCM findings and systemic Amyloidosis. *Avetisov SE, Surnina ZV, Zinovyeva OE, Safiulina EI, Shcheglova NS, Nosovsky AM. Sostoyanie nervnykh volokon rogovitsy pri sistemnom amiloidoze [State of corneal nerve fibers in systemic amyloidosis]. Vestn Oftalmol. 2021;137 (5. Vyp. 2):231-237. Russian. doi: 10.17116/oftalma2021137052231. PMID: 34669332. + Thimm A, Carpinteiro A, Oubari S, Papathanasiou M, Kessler L, Rischpler C, Malik RA, Reinhardt HC, Rassaf T, Herrmann K, Kleinschnitz C, Stettner M, Hagenacker T. Corneal confocal microscopy to detect early immune-mediated small nerve fiber loss in AL amyloidosis. Ann Clin Transl Neurol. 2022 Jun; 9(6):853-863. doi: 10.1002/acn3.51565. Epub 2022 Apr 30. PMID: 35488792; PMCID: PMC9186132

Table 6: IVCM and neuropathies

Name of author	Type of study	Population	Aim	Result	Conclusion
Keskiner-Ozturk E *et al*. *	Cross sectional	15 patients with Chronic inflammatory demyelinating poly neuropathy (CIDP) and 31 healthy subjects	To investigate the potential role of IVCM in patients with CIDP	CNFD and CNFL were significantly lower in patients with CIDP compared to healthy subjects.	This could serve as a non-invasive biomarker in demyelinating polyneuropathies.
Fleischer M *et al*. +	Cross sectional	10 CIDP patients with and 45 CIDP patients without DM, 28 Diabetic patients with and 30 Diabetic patients without Diabetic neuropathy. 58 healthy controls	To study if IVCM can distinguish CIDP from Diabetic neuropathy and identify CIDP in patients with co-existing DM	CNFD, CNFL and CBFD were reduced in CIDP, Diabetic neuropathy, and CIDP with Diabetic neuropathy. However, increased dendritic cell density in proximity to corneal nerves identifies patients with CIDP.	IVCM can thus help to differentiate between inflammatory and non-inflammatory polyneuropathies
Petropoulos IN *et al*. ++	Cross sectional	29 Diabetic peripheral neuropathy (DPN) patients, 34 CIDP, 13 Chemotherapy induced peripheral neuropathy (CIPN), 14 HIV associated sensory neuropathy (HIV SN), and 20 healthy controls	To assess CNFL, CNFD and corneal nerve fiber fractal dimension analysis (CNFrD) in patients with various neuropathies	CNFD was reduced in all neuropathies compared to healthy controls. CNFrD (a topological assessment of the main nerve fiber and its branches) revealed lowering in all neuropathies compared to healthy controls but the greatest reduction was noted in Diabetic neuropathy, followed by CIPN, CIDP and HIV- SN.	Assessment of corneal nerve topology can help in distinguishing the different types of neuropathies.

IVCM findings in neuropathies. *Keskiner-Ozturk E, Akkaya-Turhan S, Toker E, Uluc K, Alibas H, Tanridag T, Kahraman-Koytak P. Corneal nerve fiber involvement in chronic inflammatory demyelinating polyneuropathy. Neurol Sci. 2023 Jul; 44(7):2509-2516. doi: 10.1007/s10072-023-06711-1. Epub 2023 Mar 1. Erratum in: Neurol Sci. 2023 Mar 9: PMID: 36856905. + Fleischer M, Lee I, Erdlenbruch F, Hinrichs L, Petropoulos IN, Malik RA, Hartung HP, Kieseier BC, Kleinschnitz C, Stettner M. Corneal confocal microscopy differentiates inflammatory from diabetic neuropathy. J Neuroinflammation. 2021 Apr 8;18(1):89. doi: 10.1186/s12974-021-02130-1. PMID: 33832507; PMCID: PMC8033689. ++ Petropoulos IN, Al-Mohammedi A, Chen X, Ferdousi M, Ponirakis G, Kemp H, Chopra R, Hau S, Schargus M, Vollert J, Sturm D, Bharani T, Kleinschnitz C, Stettner M, Peto T, Maier C, Rice ASC, Malik RA. The Utility of Corneal Nerve Fractal Dimension Analysis in Peripheral Neuropathies of Different Etiology. Transl Vis Sci Technol. 2020 Aug 28;9(9):43. doi: 10.1167/tvst.9.9.43. PMID: 32934893; PMCID: PMC7463182

of cognitive and motor impairment as well.[20,21] Other than stromal nerve changes, intraepidermal nerve density was also found to be reduced in these patients.[20] Corneal nerve parameters were also noted to be worse in the PD subtype with postural instability and gait disturbance compared to the tremor subtype, thus it could help in the segregation of different subtypes of PD.[22] IVCM, examination thus serves as a handy tool that can help predict neurodegeneration in patients with PD. In theses patients with tremors and mobility problems, this simple examination method could probably serve as a prognostic guide, sparing the patient and the doctor more elaborate and invasive procedures. However further studies are needed to quantify IVCM changes in PD and its subtypes and also correlation with other regularly used investigations is needed.

Migraine is a complex brain disorder, characterized by recurrent attacks of disabling headaches, often associated with sensory, motor and autonomic disturbances.[23] Three studies analyzing corneal nerve changes in Migraine were included in this review. [Table 3] CNFD, CNFL, and CNBD were all noted to be reduced, and the interesting observation was that these parameters were noted to be especially worse in chronic migraine.[24-26] Similarly corneal nerve parameters were noted to be reduced and more so in patients having migraine with photophobia, compared to migraines without photophobia.

Table 7: IVCM and miscellaneous conditions

Name of author	Type of study	Population	Aim	Result	Conclusion
Bussan KA *et al*. *	Cross sectional study	76	To ascertain a potential relationship between obstructive sleep apnoea and morphology and sensitivity of corneal nerves and the relationship with severity of obstructive sleep apnea	No significant association was noted between Obstructive sleep apnea and corneal nerve plexus changes.	The corneal nerve plexus was unaffected in patients with Obstructive sleep apnoea
Waszczykowska A *et al*. +	Observational case series	12 patients with biallelic mutation in the WFS1 gene and 30 controls with Type 1 DM	To assess the corneal nerve pattern in patients with Wolfram syndrome	There was decreased corneal sensitivity and reduction in CNFL, CBFD and CNFD.	There was a reduction in corneal sensitivity with corneal nerve degeneration and this correlated with disease progression in Wolfram syndrome
Khan A *et al*. ++	Cross sectional	15	To assess the corneal nerve morphology in Autism spectrum disorder compared to normal subjects using IVCM	IVCM shows significant lowering of corneal nerve fiber density, nerve fiber length, branch fiber density and nerve fiber tortuosity in autism spectrum children compared to healthy controls	This simple test could serve as a biomarker for disease progression

The above table shows IVCM findings in Obstructive sleep pane, Wolfram syndrome and Autism. *Bussan KA, Stuard WL, Mussi N, Lee W, Whitson JT, Issioui Y, Rowe AA, Wert KJ, Robertson DM. Differential effects of obstructive sleep apnea on the corneal subbasal nerve plexus and retinal nerve fiber layer. PLoS One. 2022 Jun 30;17(6):e0266483. doi: 10.1371/journal.pone. 0266483. PMID: 35771778; PMCID: PMC9246161. + Waszczykowska A, Zmysłowska A, Bartosiewicz K, Studzian M, Pułaski Ł, Braun M, Ivask M, Koks S, Jurowski P, Młynarski W. Reduced Corneal Sensitivity with Neuronal Degeneration is a Novel Clinical Feature in Wolfram Syndrome. Am J Ophthalmol. 2022 Apr; 236:63-68. doi: 10.1016/j.ajo. 2021.09.030. Epub 2021 Oct 26. PMID: 34710353. ++ Khan A, Kamal M, Alhothi A, Gad H, Adan MA, Ponirakis G, Petropoulos IN, Malik RA. Corneal confocal microscopy demonstrates sensory nerve loss in children with autism spectrum disorder. PLoS One. 2023 Jul 12;18(7):e0288399. doi: 10.1371/journal.pone. 0288399. PMID: 37437060; PMCID: PMC10337936

All these studies highlight the neurological basis of migraine and its association with changes in the nervous system beyond the brain. The role of the trigeminal nervous system in the pathogenesis of migraine is further highlighted in these studies.

Another relatively newer addition to the IVCM corneal nerve alterations in recent times are those due to COVID-19 infections, especially long COVID. Clinical data shows that although COVID-19, which was originally considered a pulmonary disease, is associated with functional impairment of one or more organs, which may persist for a long time, hence acquiring the label of post-COVID or long COVID.[27] CNFD, CNFL, and CNBD were reduced in post-COVID patients, [Table 4] compared to healthy controls and there was also an increase in dendritic cell counts in the stroma.[28,29] Corneal peripheral nerves were also affected by COVID-19.[30] These findings probably underline the inflammatory basis of the nerve damage in long COVID. Corneal nerve damage could be one of the factors involved in the pathogenesis of post-COVID dry eye syndrome and it also alerts clinicians to the possibility of developing extraocular neuropathies.

The corneal nerves have been closely studied in Amyloidosis, a multisystem disease with fibrillary protein deposition in various organs and subsequent organ damage.[31] Amyloidosis is a condition known to cause polyneuropathy. [Table 5] Increased corneal nerve tortuosity and reduction in CNFD and CNFL were noted, thus helping in early detection on nerve fiber damage non-invasively.[32,33]

The corneal nerves were assessed in various types of polyneuropathies [Table 6] like Chronic inflammatory demyelinating polyneuropathies (CIDP), chemotherapy induced peripheral neuropathy (CIPN) and HIV-associated sensory neuropathy (HIV-SN). Keskiner-Ozturk *et al.* noted that CNFD and CNFL were lower in CIDP patients compared to healthy controls whereas Fleischer *et al.* noted reduction in CNBD as well.[34,35] Similar reductions were noted in Diabetic neuropathy also, but CIDP demonstrated an increase in dendritic cell in the perineural area. CNFD was lowered in all types of neuropathies.[36] CNFrD (a topological assessment of the main nerve fiber and its branches) revealed a lowering in all neuropathies compared to healthy controls but the greatest reduction was noted in Diabetic neuropathy, followed by CIPN, CIDP, and HIV-SN.

IVCM analysis of certain other conditions were also included in this review. [Table 7] The IVCM parameters were normal in Obstructive sleep apnoea patients.[37] Patients with Wolfram disease showed a reduction in CNFL, CNFD, and CNBD.[38] Children with autism spectrum disorder also showed a reduction in corneal parameters (CNFD, CNBD, CNFL, and nerve fiber tortuosity).[39]

IVCM examination of corneal nerves thus provides a very useful tool in the armamentarium of the ophthalmologist to assess the condition of the nervous system in general. IVCM examination of corneal nerves has great scope as a screening tool for patients prone to develop neuropathies and also

in monitoring the progression of neuropathies and certain neurological conditions. Knowledge of the anatomy and layout of the corneal nerves is often overlooked in ophthalmology teaching and it should be included in undergraduate and postgraduate ophthalmology teaching and the importance of this simple examination should be stressed upon.

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Conflicts of interest

There are no conflicts of interest.

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"There's something in the corner of my eye"



Figure 1: Photo of the eye under diffuse illumination

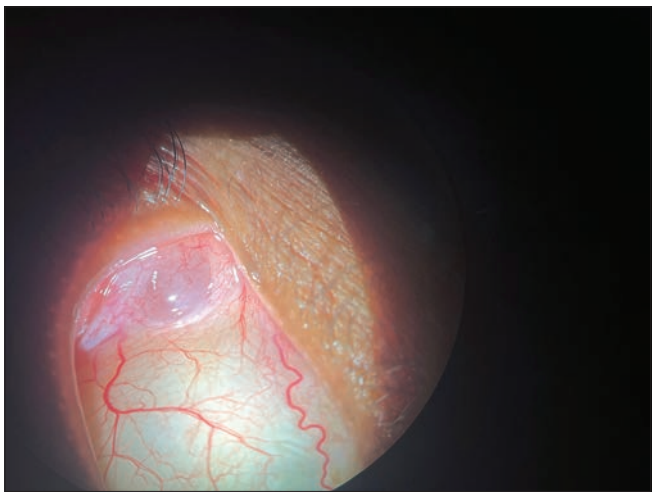


Figure 2: Magnified image of the swelling

A 53-year-old female presented to the OPD with complaint of an incidentally noted swelling on the lateral aspect of her left eye. She did not complain of pain and stated that the swelling slightly increased in size whenever she used to cry. On examination, a hemispherical non-tender cystic bluish swelling of size 5 mm × 5 mm and smooth surface was noted on the lateral aspect of the upper fornix of her left eye. There was no proptosis or ptosis, and her extraocular movements were full. Rest of her examination was within normal limits in both eyes. The clinical photographs are shown in Figures 1 and 2.

Question: What is the clinical diagnosis?

A. Dacryops
B. Frontal Sinus Mucocele
C. Dermoid Cyst
D. Extraocular Muscle Cyst

Answer: Dacryops

Dacryops is also known as lacrimal gland cyst and is a fluid-filled cyst found to be associated with the lacrimal gland. It is a rare clinical condition with trachoma suggested to be the most common etiology. Various pathogenesis have been postulated such as obstruction of the ducts of the lacrimal gland[1] and that of hypersecretion of IgA into the duct lumen followed by the osmotic retention of water leading to the formation of the cyst.[2,3] Histologically, the lesion is a fluid-filled cyst with its wall having a lining epithelium that is generally devoid of any features of atypia; hence, these swellings are benign. The condition is a clinical clincher; hence, further investigations are not mandatory. However, the extent and nature of the swelling can be confirmed with a CT or ultrasonogram. If asymptomatic, these lesions may be left alone due to their benign nature. However, in the context of ocular irritation or poor cosmesis, either a surgical excision of the cyst or marsupialization of the cyst can be done.[2] Schirmer's test can be used to determine the type of surgical procedure – if the tear production is low, marsupialization can be preferred over surgical excision to avoid the possibility of the patient postoperatively ending in aqueous tear deficiency dry eye.[2] The surgical approach is usually transconjunctival. Incomplete excision of the cyst may cause recurrences. Possible complications of an untreated cyst can be secondary infection and fistulization. Malignant transformation of the cyst is extremely rare with there being only one reported case of malignant transformation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Death on the surgical table: Medicolegal implications for doctors

INTRODUCTION

The criminal liability in cases of medical negligence is primarily governed by the provisions of the Indian Penal Code, 1860 (IPC). While the IPC does not explicitly define "medical negligence," it provides a legal basis for holding healthcare professionals criminally liable for their actions or omissions. In this article, we primarily deal with criminal liability of a doctor in the event of death of a patient on the surgical table.

Case Scenario: Salient points and defenses

Let us take the illustrative situation where a six year old boy undergoes squint surgery under general anesthesia. Soon after induction of anesthesia, the boy dies because of cardiac arrest. What is the medical liability?

The doctor in question can have both civil and criminal liability if medical negligence is proven.

Notably, Section 304A of the IPC deals with cases involving the death of a person due to a rash or negligent act. This provision is frequently invoked in cases of medical negligence, leading to a patient's demise, and can result in imprisonment for up to 2 years. Additionally, other general provisions of the IPC, such as Section 337 (causing hurt) and Section 338 (causing grievous hurt), are also utilized in the context of medical negligence cases. The distinction between civil and criminal liability hinges on the degree of negligence, with criminal liability typically requiring a higher threshold of recklessness or gross negligence.

Defenses for doctors

Keeping in view the rise in criminal prosecution of doctors, which is both embarrassing and harassing for them, and to protect them from unjust prosecutions, Supreme Court (Jacob Mathew vs State of Punjab) laid certain binding guidelines till statutory rules or instructions by the government in consultation with MCI are issued, which are as follows:

1. Private complaints may not be entertained unless the complainant has produced prima facie evidence in the court in the form of a credible opinion given by another competent doctor.
2. The investigation officer should obtain an independent and competent medical opinion preferably from a doctor in government service qualified in that branch of medical practice who can normally be expected to give an impartial and unbiased opinion applying Bolam test (what an average doctor would have done in a similar situation) to the facts collected in the investigation.
3. There should have been gross negligence from the side of the doctor.
4. The doctor may not be arrested in a routine manner unless the arrest is necessary for furthering the investigation or for collecting the evidence or if the investigation officer is satisfied that the doctor may flee.[1]

However, instances of the media trial are difficult to combat. The best doctors can do is present their counter arguments in the media and file a defamation suit against the media house once the case is judged in their favor.

What is new?

From July 2024, the Indian Penal Code (IPC) is being replaced by Bhartiya Nyaya Sanhita (BNS). The corresponding section for 304A IPC is section 104 in BNS.[2] Doctors are not exempt from criminal liability even in this new law. According to section 104 of BNS, the punishment is enhanced to 5 years imprisonment in comparison to 2 years imprisonment as in 304A IPC for a normal person. But for a registered medical practitioner recognized by the national medical council, this punishment is reduced to 2 years with a mandatory fine (according to the new law, BNS). This is the only leniency given to doctors.

Take home messages

1. Doctors can be held accountable for criminal negligence. It is very important that a doctor is aware of his rights when he faces criminal prosecution.
2. A doctor has two safeguards under section 304A of IPC in comparison to a normal person:
   a. Not mere negligence but gross negligence has to be proven against the doctor.
   b. The negligence has to be substantiated by a competent doctor in the same field before arrest and prosecution.
3. The correct section under which a doctor can be booked in cases of medical negligence leading to a patient's demise is 304A IPC, which is bailable. Law enforcing agencies may erroneously book a doctor under section 304 IPC, which is culpable homicide and nonbailable. One has to be vigilant to detect and defend against such flaws.
4. Remember: Vigalantibus Non Dormientibus Jura Subveniunt – "Law assists only the Vigilant".

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Mask-associated dry eyes in Indian population: A patient-reported web-based survey

ABSTRACT

Purpose: To present the outcomes of the mask-associated dry eyes (MADE) survey in an Indian scenario. **Methods:** An online survey was conducted amongst general population from May to July 2021 to assess the burden of dry eyes and MADE. To summarize the findings, descriptive statistics were employed, and statistical significance was determined between various mask practices and dry eye symptoms. A *P* value of <0.05 was considered statistically significant. **Results:** Four hundred and ten respondents are participated in this survey. Almost two third of patients (62.3%) used masks every day, and 50.7% wore them for more than six hours. Approximately 36% never experienced dry eye, 24% experienced it occasionally, and 41% experienced dry eye symptoms, with seven percent of patients experiencing it regularly. Around 30% of patients feel their symptoms started after they used the mask, whereas 70% believed that they existed before. About half of the patients (51.5%) feel that wearing the mask made their symptoms worse. Dryness symptoms, higher lubricant usage, and difficulties with air conditioning were found to be statistically significant when the frequency and hours of mask wear were increased. Furthermore, an increase in screen time was linked to an increase in eye tiredness ($P = 0.018$). **Conclusion:** The survey demonstrates that increased frequency and hours of mask usage leads to a worsening of dry eye symptoms. Additionally, worsening of eye tiredness was associated with increased screen time. The survey results are important for fellow ophthalmologists to better understand the impact of MADE on the quality of life of general population. This can be utilized to counsel the patients regarding the preventive and supportive eye care.

Keywords: COVID-19, dry eyes, mask-associated dry eyes

INTRODUCTION

COVID-19 has become the most severe public health danger associated with a respiratory virus since the outbreak of the H1N1 influenza pandemic, causing hundreds of thousands of deaths and infecting millions of people worldwide. COVID-19 has led in 5 million deaths since its emergence in December 2019.[1] The WHO has mandated the use of masks (medical or surgical masks, N-95 respirators, or similar) as personal protective means to combat COVID-19. Self-protection is regarded to be the most effective method of infection prevention and management. As a result, despite breakthroughs in pharmacology and vaccinations, self-protection with masks and face shields is vital in order to protect ourselves from COVID-19.

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COVID-19 has been associated with a multitude of ocular manifestations in both the anterior and posterior segment.[2,3] Among these, dry eyes have emerged as a major public health issue, particularly as a result of increased screen time and mask use. The mask limits the spread of air and the exhaled air moves upwards creating an air current over the cornea, leading to increased evaporation of the tear film, which leads to dry spots on the ocular surface, eye irritation, and discomfort.[4,5] The contact between the warmer exhaled air and the cooler glasses lenses leads to condensation and the formation of

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small water droplets that scatter light, reduce visual acuity, and negatively affect vision.[6] The tear film and ocular surface dry eye workshop II (TFOS DEWS II) report defines dry eye disease (DED) as a multifactorial disease of the ocular surface featured by a loss of homeostasis of the tear film, associated ocular symptoms, in which tear film instability and hyper osmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[7]

Mask-associated dry eye (MADE) was first observed in June 2020, when White, an American ophthalmologist, published it on his blog and coined the abbreviation "MADE."[8] MADE can worsen dry eye symptoms in pre-existing dry eye or postmenopausal dry eye; digital screen users for long hours; elderly men or postmenopausal women; post-cataract IOL surgery cases; post-Lasik cases; contact lens wearers, having a lower-quality corneal tear film; and masked people with history of work for long hours in air-conditioned settings and/or using digital screens. To prevent the occurrence or worsening of dry eyes, care should be taken to use topical lubrication along with eye protection in conjunction with the mask. Additional caution is also advised for patients with a prior history of dry eye disease, recent ophthalmic surgery, or other surface inflammatory diseases, such as Sjogren syndrome while using masks for extended periods.

A recent review indicated a marked increase in dry eye symptoms in patients upon starting to wear a face mask during this pandemic outbreak.[9] This study was conducted out to document the burden of MADE among adults in India, given the impact of DED on the quality of life (QoL) and healthcare expenditures, and the lack of published data in India. An online survey was used to analyze the occurrence and worsening of dry eye symptoms in general population who used masks on a regular basis.

MATERIALS AND METHODS

An independent ethical review board was conducted and this study conforms to the principles and applicable guidelines for the protection of human subjects in biomedical research. The study was conducted as an online survey, asking general population to contribute to the research by completing the questionnaire. This questionnaire was created after studying comparable surveys used for DED. Questions were rephrased in a neutral manner to elicit useful information from the general public. A panel of two specialists (AK, PM) with experience in ocular surface disorders examined and agreed on these tailored questions. Data were collected from May 2021 to July, 2021. Participants were asked to respond about their demographic characteristics. The detailed questionnaire is provided as Annexure 1.

Descriptive statistics were used to summarize the results, and statistical significance was analyzed between the various mask practice and the dry eye symptoms. $P<0.05$ was taken as statistically significant

RESULTS

In total, 410 responses were analyzed. The participants' age ranged from 17 to 77 years. Fourty nine percent were males and 51% were females.

Approximately, two third of patients (62.3%) wore mask on almost all days, and 50.7% used masks continuously for more than six hours. About 36% never experienced dry eye, 24% rarely experienced dry eye, and 41% experienced dry eye symptoms of which seven percent experienced it frequently. About 30% of patients believed their symptoms began after using the mask, while 70% believed they existed prior to using the mask. Approximately half of the patients (51.5%) believed that wearing the mask aggravated their symptoms. Approximately 43% have used a visual display screen for more than six hours, and 36% have used artificial tears at some point in time.

Among the various mask related risk factors evaluated, increased frequency and hours of mask use were found to be statistically significant associated with the symptoms of dryness, increased lubricant use, and difficulty in air-conditioning. Moreover, an increased screen time was significantly associated with increased tiredness of eyes ($P = 0.018$). Table 1 illustrates the relationship between the mask-related risk factors and the symptoms of dry eyes.

DISCUSSION

The study's goal was to look at the occurrence and exacerbation of dry eye symptoms in those who used masks on a daily basis. We noted a worsening of dry eye symptoms with increased hours and frequency of mask usage. Additionally, increased tiredness of eyes was related to the increased screen time.

The escape of the exhaled air, with a temperature of approximately 36°C–37°C, which flows through the upper edge of the mask toward the ocular surface, is the essential reason for the occurrence of MADE. Despite the fact that it is emerging as an important ocular surface condition as a result of the extensive use of masks on a global scale, there is a paucity of information on MADE. We could find from our study that the main factors contributing to the MADE were the increased frequency and increased duration of mask use. The increased airflow accelerating the evaporation of the tear

Table 1: Showing the statistical significance various mask related risk factors and dry eye symptoms

	P			
	Symptoms of dry eye	**Increased lubricant use**	**Difficulty in air conditioning**	**Tiredness of eyes**
Increased frequency of mask use	*P*=0.036	*P*=0.019	*P*=0.00	*P*>0.05
Increased hours of mask use	*P*=0.020	*P*=0.003	*P*=0.00	*P*>0.05
Increased screen time	*P*>0.05	*P*>0.05	*P*>0.05	*P*=0.018

film continuously for hours or days, resulting in ocular surface irritation or inflammation could be the underlying reason.

In our study, 41% of the participants experienced dry eye symptoms. This is lower than around 64% reported in a similar study by Boccardol.[9] In our study, 30% of the participants experienced the onset of dry eye symptoms after the use of mask which is also much lower than approximately 50% of the responders in the survey conducted by Boccardo.[9] Disruption of the corneal neuronal network has been reported in patients with DED.[10]

A recent study by Tagawa *et al*.[11] demonstrated the corneal hyperalgesia in DED patients with short tear film breakup time. The fact is some individuals with dry eyes may be more sensitive to noticing these symptoms may explain the variation in DED symptoms observed in our study from the literature.

According to the results of our survey, around 42% of participants used digital devices for more than six hours per day, and higher screen time was significantly related to tired eyes in our study. Bahkir and Grandee[12] surveyed 407 people (average age 27.4 years) through social media platforms and found that the average increase in screen time during lockdown was 4.8 6 +/− 2.8 hours per day, resulting in an average screen time usage of 8.65 +/− 3.74 hours. The decreased blink rate is likely the primary mechanism by which electronic device use worsens dry eye. Fortunately, some, if not all, of the increase in dry eye disease associated with digital device use is reversible. In 2014, Moon *et al*.[13] studied smartphone use and dry eye signs and symptoms in children in South Korea and found that both signs and symptoms resolved after four weeks of screen time cessation.

There are numerous recommendations for dealing with MADE, especially for individuals using masks for extended periods and for patients with a prior history of dry eye disease: Use of lubricant eye drops and eye protection, such as goggles, in conjunction with the masks, paying special attention should be given to the correct fitting of the mask to prevent air being directed toward the eyes, taping the mask at the top to impede upward airflow, and taking adequate breaks to remove the mask, allowing the eyes to recover, and reapplying lubricant eye drops.

The major limitation of the current study is the lack of use of a standardized questionnaire for evaluation and it is internet-based nature which prevented participants with no internet access from the participating in the study. Additionally, the analysis is primarily descriptive in nature. Nonetheless, this is the first Indian data on the burden of MADE in India. Further studies with the standardized questionnaire along with a detailed clinical evaluation are warranted to validate our results.

To conclude, in our study we observed a worsening of dry eye symptoms as the number of hours and frequency of mask use increased. Furthermore, increasing screen time was associated with increased eye tiredness. Thus, changes in everyday behaviors brought on by the pandemic may aggravate dry eye symptoms and reduce quality of life. We encourage our fellow ophthalmologists to be aware of MADE, to counsel patients about the necessary preventive and supportive eye care, and to continue to monitor this emerging entity.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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ANNEXURE 1

Survey Questionnaire

What is the frequency of mask use? - On all days/occasionally

How many hours of mask use per day? – More than or less than 6 hours

Is the use of mask continuous? Yes/No

How often do you feel eye dryness?

Have you experienced light sensitivity?

How often do your eyes feel gritty (FB sensation inside the eye)?

Do you have tired eyes?

How often do you have blurred vision (not seeing clearly)?

Do you feel uncomfortable while reading? (Painful or Tired eyes)

Do you feel uncomfortable while driving at night?

Do you feel uncomfortable while watching TV/Computer/LED Screen?

Do you feel tiredness of eyes in air conditioned rooms?

Does sudden weather changes affect your dry eye symptoms?

And the participants were asked to respond by selecting either of the options –Never, Sometimes, Half of the time, Most of the time, or Always.

Original Article

Validation of using smartphone based non-mydriatic camera for retinal photography to diagnose diabetic retinopathy

ABSTRACT

Purpose: To assess the sensitivity and specificity of retinal imaging captured by portable non-mydriatic 'fundus on phone' camera as a screening tool against the conventional seven field digital fundus photography. **Design:** Prospective comparative study design. **Methods:** Study was performed over 300 diabetic patients (600 eyes). First fundus pictures were taken with non-mydriatic 'fundus-on-phone' camera and then with Zeiss seven field fundus camera after pupillary dilation. Images were analysed and compared by two observers. **Results:** Out of all the 600 undilated fundus images, 15.5% were ungradable, 76% were graded as poor and average quality by both observers. From the dilated fundus images taken using Zeiss camera, only 0.8% images were found ungradable by both observers. The sensitivity and specificity for detecting any diabetic retinopathy changes and its severity by using 'fundus-on-phone' camera against Zeiss fundus camera were found to be 54.92% and 85.5%, respectively, by observer one and 56.48% and 85.5%, respectively, by observer two. **Conclusion:** Non-mydriatic retinal imaging using fundus-on-phone camera is not a feasible method for screening diabetic retinopathy due to low sensitivity and high number of poor-quality images.

Keywords: Diabetic retinopathy screening, fundus on phone camera, non-mydriatic retinal imaging, smartphone fundus camera, zeiss fundus camera

INTRODUCTION

Diabetic retinopathy (DR) is one of the important causes for blindness in adults with diabetes with its worldwide prevalence estimated to be around 27% between 2015 to 2019.[1,2] 65 million diabetics are living in India[3] and diabetic retinopathy prevalence is estimated to be 16.9%.[4]

As per Govt. of India guidelines, National program for prevention and control of cancer, diabetes, cardiovascular disease and stroke (NPCDCS) recommends annual screening of all diabetic patients for Diabetic retinopathy.[5] This translates to over 65 million Indians with diabetes need to be screened for diabetic retinopathy every year.

The gold standard for screening for diabetic retinopathy is use of mydriatic seven field stereoscopic retinal colour photography.[6] However, the limiting factors for screening large numbers of people with diabetes include lack of adequate number of ophthalmologists, trained eye technicians and lastly non-availability of fundus cameras below sub-district level.

This study utilizes an indigenous, sleek smart phone-based non-mydriatic device for capturing retinal colour photography which can be used for screening of diabetic retinopathy.

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MATERIALS AND METHODS

A comparative descriptive study was conducted over 600 eyes of 300 consecutive diabetic patients attending OPD at a South Indian tertiary care centre. The study was approved by Ethical Committee of our institute. A written informed consent was obtained from all the participants. The study followed declaration of Helsinki.

The inclusion criteria were age more than 18 years, of either sex with type I and II diabetes. The exclusion criteria were those patients who are contraindicated for mydriasis or have allergy to Tropicamide and Phenylephrine eye drops or those with significant media opacity (e.g., cataract, central corneal opacity, etc.) which hinders retinal imaging or having co-existing retinal pathologies such as retinal degeneration or age-related macular degeneration.

A fixed protocol was followed for all patients. Complete ophthalmic examination which includes recording visual acuity, anterior segment evaluation and non-contact tonometry was done following which undilated fundus photograph was taken using non-mydriatic (test) fundus camera. The entry of patients' data followed by image capturing using the non-mydriatic camera took approximately 10-15 minutes. The pupils were then dilated, and fundus photograph was again taken with conventional dilated fundus camera.

Here, non-mydriatic fundus images were taken using 'fundus-on-phone' (FOP) retinal imaging system (Remidio Innovative Solutions Pvt. Ltd, Bangalore) which consists of a smart phone attached to the FOP device [Figure 1]. It enables to take four field retinal colour photography which includes macula, optic disc and nasal to optic disc, superotemporal and inferotemporal quadrants to provide 40°-45° field of view in each image and up to 12x magnification. The FOP is a compact, portable device featuring annular illumination to eliminate artifacts and specular reflections thus producing high quality reflex free images. The device is cloud-synchronized that enables images to be achieved and stored on the cloud for remote review of images.

After taking undilated images, pupils were dilated using mydriatic drugs (Tropicamide 0.8% + Phenylephrine 5% combination) and conventional seven field digital fundus photographs were taken using ZEISS VISUCAM fundus camera [Figure 2]. It consists of 24-megapixel sensor with Zeiss optics enabling ultra-high resolution reproducible imaging for every patient.

All undilated and dilated fundus images were taken by a post-graduate student in ophthalmology and were coded using an identification number. Images were analysed for presence and severity of diabetic retinopathy. Grading of DR was done based on modified Early Treatment Diabetic Retinopathy Study (ETDRS) grading system.[6] Both the images were analysed, compared and graded by two ophthalmologists (observer-one and observer-two) who remained constant throughout the study and were masked to clinical diagnosis.

Image quality grading[7]

Grade 0- Ungradable (No details visible).

Grade 1- Poor (Only gross haemorrhages/dense exudate visible).

Grade 2- Average (Major retinopathy details visible; microaneurysm, IRMA, NVE not clear).

Grade 3- Good (Most retinopathy changes seen).

Grade 4- Excellent (All lesions clearly visible).



Figure 1: Fundus on Phone (FOP) camera



Figure 2: Zeiss Visucam fundus camera

Statistical analysis

All statistical analyses were performed using SPSS statistical package version 15.0. Continuous data were expressed as mean ± standard deviation while categorical data were presented as proportions. The sensitivity and specificity for detecting DR and diagnosing DR of varying degrees of severity were calculated for the FOP taking the dilated seven field fundus photography by the traditional Zeiss fundus camera as the gold standard. The degree of agreement between FOP and gold standard Zeiss seven field fundus photography were quantified using specific formulas for sensitivity and specificity. This was done for both observers separately.

RESULTS

A total of 300 patients (600 eyes), 173 (57.7%) males and 127 (42.3%) females were included in the study. Mean age of participants was 57.36 ± 9.406 years and mean duration of diabetes mellitus was 8.03 ± 5.478 years.

Out of 600 images of undilated fundus taken using FOP camera, only 51 (8.5%) images were graded as three and four by both observers, while 93 (15.5%) images were considered ungradable by both observers. Majority of images (76%) were graded as grade one and two (i.e., poor and average) by both observers. Comparison of images from non-mydriatic fundus camera and mydriatic Zeiss camera is given in Figures 3 and 4.

From the undilated images, no DR was found in 435 (72.5%) images by observer one and 432 (72.0%) images by observer-two [Table 1]. Among those found to have DR were further divided into those having Mild Non-proliferative Diabetic Retinopathy (NPDR), Moderate NPDR, Severe NPDR and Proliferative Diabetic Retinopathy (PDR). A high percentage of similarity was found in grading of undilated images by two observers was found.

While among the dilated fundus images taken by Zeiss fundus camera, 407 (67.9%) images were found to have no DR changes by both the observers. Grading of dilated images also showed good amount of similarity between the two observers with five (0.8%) images being classified as ungradable by both observers.

Presence or absence of DR and its severity in undilated and dilated images was graded by each observer [Tables 2 and 3]. No DR was found in 348 images by both undilated and dilated fundus photography as observed by observer-one, while DR was found in 106 images by both methods [Table 4].

Of all images evaluated by observer-two, 348 images were matched as having No DR changes by both undilated and dilated imaging, while 109 images were matched to have DR changes [Table 5]. Only four images were found ungradable by both undilated and dilated methods by both observers.

For sensitivity and specificity, dilated (considered gold standard here) and undilated fundus images were compared.

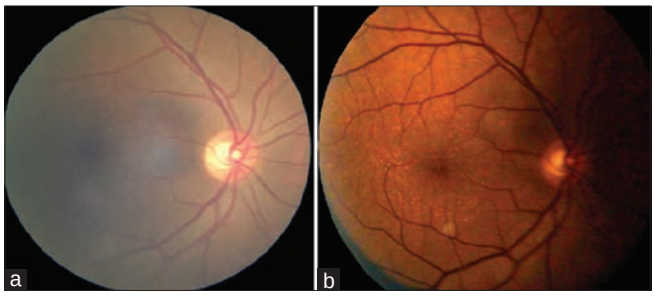


Figure 3: (a) Undilated and (b) Dilated fundus images of case no 5

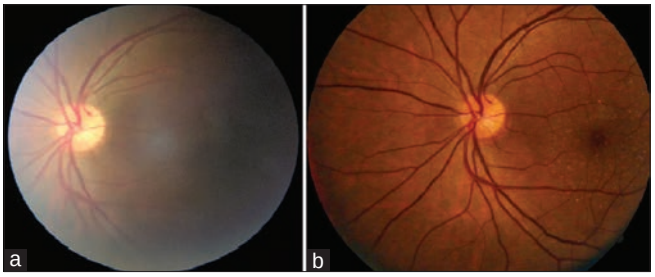


Figure 4: (a) Undilated and (b) Dilated fundus images of case no 22

Table 1: Grading of undilated and dilated fundus images by observer-1 and 2

	Observer-1				Observer-2			
	Undilated		Dilated		Undilated		Dilated	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
No DR	435	72.5	407	67.9	432	72.0	407	67.9
Mild NPDR	35	5.8	59	9.8	34	5.7	57	9.5
Moderate NPDR	22	3.7	58	9.7	26	4.3	59	9.8
Severe NPDR	8	1.3	39	6.5	8	1.3	40	6.7
PDR	7	1.2	32	5.3	7	1.2	32	5.3
Ungradable	93	15.5	5	0.8	93	15.5	5	0.8
Total	600	100	600	100	600	100	600	100

DR=Diabetic Retinopathy, NPDR=Non-proliferative Diabetic Retinopathy, PDR=Proliferative Diabetic Retinopathy

Table 2: Distribution of absence or presence of diabetic retinopathy and its severity as assessed by the observer-1 undilated vs observer-1 dilated cross tabulation

	Observer-1 DILATED opinion						
	No DR	Mild NPDR	Mod NPDR	Severe NPDR	PDR	Un-gradable	Total
Observer-1 UNDILATED opinion							
No DR	348	38	26	13	10	0	435
Mild NPDR	4	9	13	6	2	1	35
Mod NPDR	1	2	11	6	2	0	22
Severe NPDR	0	0	0	6	2	0	8
PDR	0	0	0	0	7	0	7
Ungradable	54	10	8	8	9	4	93
Total	407	59	58	39	32	5	600

DR=Diabetic Retinopathy, NPDR=Non-proliferative Diabetic Retinopathy, PDR=Proliferative Diabetic Retinopathy

Table 3: Distribution of absence or presence of diabetic retinopathy and its severity as assessed by the observer-2 undilated vs observer-2 dilated cross tabulation

	Observer-2 DILATED opinion						
	No DR	Mild NPDR	Mod NPDR	Severe NPDR	PDR	Un-gradable	Total
Observer-2 UNDILATED opinion							
No DR	348	38	26	13	10	0	435
Mild NPDR	4	9	13	6	2	1	35
Moderate NPDR	1	2	11	6	2	0	22
Severe NPDR	0	0	0	6	2	0	8
PDR	0	0	0	0	7	0	7
Ungradable	54	10	8	8	9	4	93
Total	407	59	58	39	32	5	600

DR=Diabetic Retinopathy, NPDR=Non-proliferative Diabetic Retinopathy, PDR=Proliferative Diabetic Retinopathy

Table 4: Distribution of absence or presence of diabetic retinopathy as assessed by the observer-1 undilated vs observer-1 dilated cross tabulation

	Observer-1 DILATED OPINION		
	No DR	DR	Total
Observer-1 UNDILATED OPINION			
No DR	348	87	435
DR	59	106	165
Total	407	193	600

DR=Diabetic Retinopathy

Table 5: Distribution of absence or presence of diabetic retinopathy as assessed by the observer-2 undilated vs observer-2 dilated cross tabulation

	Observer-2 DILATED OPINION		
	No DR	DR	Total
Observer-2 UNDILATED OPINION			
NO DR	348	84	432
DR	59	109	168
Total	407	193	600

DR=Diabetic Retinopathy

The sensitivity and specificity for finding any DR changes and its severity by FOP camera using undilated images against Zeiss camera using dilated images were found to be 54.92% and 85.5%, respectively, as graded by observer-one and 56.48% and 85.5%, respectively, as graded by observer-two [Table 6]. This mismatch in diagnosis between 'FOP' images and Zeiss camera images by both observers was mainly found between those with No DR and those with mild OR moderate DR changes. This is justified as undilated fundus imaging with FOP camera might miss the findings of DR (e.g., microaneuryms, hard exudates, haemorrhages) which are predominantly found in mid-peripheral retina in early stages.

DISCUSSION

Nearly, 80% of people with diabetes are in developing countries like India and China where its burden is alarming.[7,8] The aim of screening is to detect retinopathy, determine its severity and to decide which patients require for further investigation and treatment. This requires a screening tool with good sensitivity and specificity.

In our study, we assessed the sensitivity and specificity of retinal imaging captured by portable non-mydriatic 'fundus on phone' camera as a screening tool for DR against the conventional seven field digital fundus photography. The idea of non-mydriatic camera as a screening tool dates back to 1980 as shown in studies done by William *et al*.[9] Non-mydriatic camera captures 40°-45° field (as against 50° field by regular camera) which as a screening tool, is sufficient to detect abnormality at the posterior pole (as in DR).

Table 6: Sensitivity and specificity of finding any DR changes by observer-1 against observer-2

	Observer-1	Observer-2
Sensitivity	54.92%	56.48%
Specificity	85.5%	85.5%
Positive predictive value	64.24%	64.88%
Negative predictive value	80%	80.56%

Grading of images by observer-one and two by non-mydriatic fundus camera showed 93 (15.5%) images as ungradable by both the observer which was comparable to that reported (12-25%) in many of the previous studies.[8-16] In a study conducted by J. Levy *et al*. on uses of mobile non-mydriatic fundus camera in primary care patients, a total of 4318 diabetic patients were screened, of whom 53% were classified as normal. In 16%, fundus picture was inadequate for assessment.[17]

Although the image quality was better with Zeiss, the FOP also had reasonably good quality gradable images but the clarity of images was poor in almost 50% patient due to inadequate pupil size, hazy media and lack of proper focusing. Early studies showed that though the specificity rates were high, sensitivity rates for the diagnosis were low, missing nearly half of cases.[18]

The sensitivity and specificity of non-mydriatic fundus camera by observer-one were 54.92% and 85.5%, respectively, and by observer-two were 56.48% and 85.5%, respectively, between the observers' observation were almost similar. Only the presence or absence of DR was compared and considered for calculation. Matching of grading of DR between two images was not done. A recent publication by Gupta *et al*.[19] to evaluate the sensitivity and specificity of non-mydriatic fundus camera as a screening tool to detect DR in Indian eyes showed a low sensitivity and specificity for detecting any DR (58.8% and 69.1%) and Sight threatening diabetic retinopathy (STDR) (63.1% and 68.9%). Factors such as longer duration of diabetes causing poor mydriasis, darker iris in Indians and older age with media opacities like cataract, affects the image quality and hence a decrease in the sensitivity and specificity of DR screening in non-mydriatic retinal imaging (NMRI).[19,20] Non-mydriatic photography is convenient, but sensitivity and specificity have always been a concern.

In a study done by Scanlon *et al*.,[21] comparing the sensitivity and specificity of mydriatic and non-mydriatic digital retinal screening, with dilated slit lamp biomicroscope as the reference standard, it showed that mydriatic digital photography was an effective method of screening for DR while non-mydriatic fundus photography had an unacceptable technical failure rate and low specificity.

FOP has several advantages: (1) time taken is less and autofocus helps to obtain sharp focus and good quality retinal images. (2) The option of zooming helps to visualize and enlarge images and capture specific retinal lesions. (3) The comfort while taking retinal images was better, as the light intensity of the LED light was lesser, and hence there was no discomfort due to high intensity flash. (4) It is cheaper, hence currently used in tele-ophthalmology. (5) Early acquisition and storage of images are possible.

The National blindness control programme lays stress on the prevention, screening and management of DR. The eleventh plan of NPCB (2007-12) emphasis the need to screen for DR, in known diabetic patients and at risk population. This highlights the proposal of putting up low-cost, portable, non-mydriatic fundus camera in diabetic clinic, which would be useful to all- physicians, ophthalmologists and the most important, patients.

Limitation

Due to pupillary size, older age, lack of proper focus and darker iris have led to the lower sensitivity of the test camera. The results could be genuine, if obtained by extending it into the community.

CONCLUSION

This study showed that a smartphone-based retinal imaging system—non-mydriatic fundus camera is not a feasible method to diagnose and detect diabetic retinopathy as a perfect tool in majority of cases. Due to high number of ungradable images, it creates unnecessary referrals for patients who do not have any DR or have only mild NPDR which necessitate an eye evaluation. A relatively low sensitivity and high rate of poor-quality photographs poses major limitation as a perfect screening tool for DR changes involving among Indian population.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Prevalence and causes of ocular morbidity among school children in urban and rural areas

ABSTRACT

Background: Poor vision impairs the performance of school children and has a negative impact on their future. The prevalence of blindness in school children is estimated to be 0.8/1000 in the age group of 0–15 years. Most children with an uncorrected refractive error are asymptomatic; hence, periodic visual screening and primary eye care reduce the prevalence of refractive error and ocular morbidity. **Objective:** To study the prevalence of ocular morbidity among school children in urban and rural areas. **Methods:** Cross-sectional study was conducted in two randomly selected private schools in urban area and two randomly selected government schools in rural area among school children aged 6–15 years studying in standards I–X. They were selected from each class by systematic random sampling. Detailed history and ocular examination were carried out for all children. **Results:** The prevalence of ocular morbidity among study participants was high (20.3%). The major cause of ocular morbidity was refractive error in 17.4% of the cases. Age group of 5–7 years, being urban school child, illiterate parents were significantly associated with ocular morbidity ($P < 0.05$). Gender and religion were not associated with ocular morbidity. The most common ocular morbidity was refractive error (17.4%). Color blindness (1.5%), conjunctivitis (1.3%), and stye and chalazion (1.1%) were other ocular morbidities. **Conclusion:** Most cases of ocular morbidity were preventable or treatable if detected early. Hence, strategies including prevention at the primary and secondary level form core of any strategies to reduce ocular morbidities in school going children.

Keywords: Morbidity, refractive error, school children

INTRODUCTION

Many ocular diseases have their origin in childhood, and the morbidity may go unnoticed and adversely affect the child's performance in school and may also cause severe ocular disability in the later part of life. In school children, vision screening should be done very effectively to detect refractive errors, the correctable cause of decreased vision. It also helps in minimizing long-term visual disability. In developing countries, children in the school going age group represent 25% of the population. Every sixth child in the world lives in India according to the statistics by the Ministry of Statistics and Program Implementation-2012.[1]

The current epidemiological data point to an increased prevalence of refractive error in children. A number of environmental factors associated with socioeconomic status and lifestyles have been reported and are widely believed to be possibly responsible for these changes. Complicated interactions between genetic predisposition and environmental exposures are also seen as important evidence for refractive errors. A study on the prevalence and pattern of ocular diseases in children is important because the majority of the causes of ocular morbidity like vitamin A deficiency and infective conditions are preventable through basic preventable measures. Also, conditions like refractive error and cataract are

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easily diagnosable with the basic investigation. Refractive error is the most common cause of visual impairment around the world and the second-leading cause of treatable blindness.[2,3]

Most children with uncorrected refractive error are asymptomatic; hence, periodic visual screening and primary eye care reduce the prevalence of refractive error.[4,5] Early detection through regular surveys helps in ensuring prompt treatment and prevention of serious complications.[6]

Therefore, the present study was carried out to study the prevalence of ocular morbidity among school children in urban and rural fields.

MATERIAL AND METHODS

The population-based cross-sectional study was conducted in two randomly selected private schools in urban area and two randomly selected government schools in rural area within a radius of 30 km from Malla Reddy Hospital in Medchal district under the guidance of Department of Ophthalmology, Malla Reddy Institute of Medical Sciences (MRIMS). The study subjects were school children aged 6 to 15 years, who were studying in standards I to X in the schools of the field practice area of MRIMS, Suraram, Rangareddy. The study was carried out over a period of one year from January 2020 to June 2021.

Institution Ethics Committee permission was obtained before the study was initiated. Permission from the District Education Officer was taken to carry out the study in the schools. The headmasters of the randomly selected schools were contacted, all details of the study were shared, and permission was sought from them. Child assent was obtained after a discussion with the children's parents about the study. All parents of children with any eye problem were informed, and they were asked to get their children to Malla Reddy Hospital for further treatment and follow-up.

School children from 6 to 15 years of age, who were studying from standards I to X, were included in the present study. School children below 6 years and above 15 years of age, children with cognitive disabilities, children with congenital multiple systemic diseases, and those not willing to give consent for the study were excluded.

Based on the previous study by Kodagu[7] taking the prevalence of ocular morbidity among school children as 20.2% with 95% confidence level, absolute precision as 5%, and design effect of 2, the sample size came out to be 496. We were actually able to include 561 children from government schools and 803 children from private schools.

A pre-tested, structured proforma was used to collect the information. After reaching the concerned school, the subjects were selected from each class by systematic random sampling, till the desired sample was met. The proforma included socio-demographic characteristics, information regarding the family type and composition, history regarding any congenital ocular deformity, deviation of eyes, trauma to eyes, blurring of vision, double vision, difficulty in differentiating colors, and history suggestive of any medication and surgical intervention. History regarding the usage of spectacles and its details are also taken with a focus on the reason for the non-usage of spectacles if present. History suggestive of symptoms like eye pain, headache, photophobia, watering of eyes, itching of eyes and scalp, discharge from eyes, any allergy, swelling or matting of eyelid was also taken. History suggestive of posterior chamber involvement like floaters and flashes of light was included in the study. A detailed ophthalmologic examination was carried out for each child.

All data were entered in MS Excel, and an appropriate statistical test was applied. Mean, standard deviation, limits, and range were calculated for the non-categorical type of data, and proportions were computed for the categorical type of data. The association of children with various ocular morbidities in urban and rural areas with respective age, gender, religion, etc., was computed by using the Chi-square test at P value <0.05 considered to be significant.

RESULTS

The prevalence of ocular morbidity in the present study was found to be 20.3% [Table 1].

The prevalence of ocular morbidity was significantly more in the age group of 5–7 years (26.3%) compared to the other two age groups. Urban school children suffered significantly more ocular morbidity compared to their rural counterparts. The prevalence of ocular morbidity was only 9.1% and 7.7% among the wards of illiterate father and mother, respectively, but it was significantly higher in their literate counterpart. The prevalence of ocular morbidity was significantly more in urban school children compared to rural school children. Gender and religion were not found to be significantly associated with ocular morbidity [Table 2].

The most common ocular morbidity was a refractive error in 17.4% of the cases. 1.5% had color blindness, and conjunctivitis was seen in 1.3%. Stye and chalazion were seen in 1.1% of cases. Other ocular morbidities like strabismus, vitamin A deficiency, nystagmus, and ocular trauma were minimal of <1% [Table 3].

DISCUSSION

The prevalence of ocular morbidity among school going children in the present study (20.31%) was comparable with the studies done in Kodagu[7] (20.2%), New Delhi[8] (22.7%), and Rural West Tripura[9], whereas studies done in Baroda[10] (14.8%), Kolar[11] (13.2%), Ahmednagar[12] (9.66%), and Mysore[13] (5.4%) showed lower prevalence. It was also noted that Vijayawada[14] and Chandigarh[15] had a higher prevalence of ocular morbidity of 34% and 30.4%, respectively. The differences in the prevalence of ocular morbidity in different studies may be due to differences in the sample size, sampling technique used, and other local geographical factors.

Table 1: Prevalence of ocular morbidity with various factors among school children

Ocular morbidity	Number	Percentage
Present	277	20.3
Absent	1087	79.7
Total	1364	100

Table 2: Association of ocular morbidity with various factors among school children

Characteristics	Ocular morbidity		Chi square	*P*
	Present	Absent		
Class				
1–4	86 (15.1%)	485 (84.9%)	19.04	<0.0001
5–7	105 (26.3%)	295 (73.7%)		
8–10	86 (21.9%)	307 (78.1%)		
Age (years)				
6–9	69 (14.9%)	395 (85.1%)	14.264	0.0007993
10–12	78 (25.3%)	230 (74.7%)		
13–15	130 (21.9%)	462 (78.1%)		
Region				
Urban	224 (27.8%)	579 (72.2%)	68.32	<0.0001
Rural	53 (9.4%)	508 (90.6%)		
Religion				
Hindu	254 (20.4%)	992 (79.6%)	0.05	0.8356
Others	23 (19.5%)	95 (80.5%)		
Father education				
Illiterate	11 (9.1%)	111 (90.9%)	9.803	0.001742
Literate	266 (21.4%)	976 (78.6%)		
Mother education				
Illiterate	12 (7.7%)	144 (92.3%)	16.45	<0.0001
Literate	265 (21.9%)	943 (88.1%)		
Gender				
Male	157 (20.9%)	595 (79.1%)	0.131	0.7174
Female	122 (19.9%)	490 (80.1%)		
Type of school				
Government	53 (19.1%)	508 (80.9%)	68.32	<0.0001
Private	224 (27.9%)	579 (72.1%)		

Table 3: Pattern of ocular morbidity among school going children

Ocular morbidity	Number	Percentage
Refractive error	237	17.4
Color blindness	21	1.5
Conjunctivitis	18	1.3
Stye and chalazion	14	1.1
Strabismus	11	0.8
Vitamin A deficiency signs	7	0.5
Nystagmus	3	0.2
Ocular trauma	1	0.07

When this prevalence was further examined to know the pattern of ocular morbidity; it showed that 237 study participants had refractive error. This constituted for 17.37% of study participants. 1.55% of the study participants were screened positive for color blindness, and 18 (1.32%) for conjunctivitis followed by 13 cases of stye and 1 case of chalazion. Strabismus, nystagmus, and ocular trauma were seen in 11, 3, and 1 cases, respectively.

Various studies showed refractive error as the most common ocular morbidity in the school going age group. Conjunctivitis ranged from 4.83% prevalence in study done in West Tripura[9] to 0.5% in study done in Kodagu[7] in 2009. It was also noted that vitamin A deficiency in the present study was low (0.5%) which was comparable with the study done in Kodagu[7] (0.74%) and Kolar[11] (0.6%), but it was less compared to Chitra Durga[16] (4.27%) and Tripura[9] (2.33%).

When study participants with ocular morbidity were analyzed according to the type of school, it was observed that the majority of them belonged to private school which constituted 80.9% of the total cases and the rest belonged to government school constituted only 19.1% of the cases. Overall prevalence in private and government schools was 27.89% and 9.45%, respectively.

The present study showed a significant number of cases of refractive error in the urban population (208 cases) compared to the rural study population (29 cases). This was found to be statistically significant ($P < 0.01$).

Among the 237 cases positive for refractive error, 51.1% complained of inability to read from the blackboard clearly. Among this, 81 (65.9%) were unaware that it was abnormal to be not able to see the blackboard. It was also seen that these students, that is, 65.9% were unaware that it can be treated. So, the present study showed a high level of ignorance regarding refractive error. Among the 237 cases of refractive error, the majority of the cases (74.27%) were newly detected cases with only 25.73% of the cases previously diagnosed.

CONCLUSION

The overall prevalence of ocular morbidity among study participants was high (20.31%). The major cause of ocular morbidity was refractive error. The majority of the cases belonged to the urban population compared to the rural population. There was an increased incidence in ocular morbidity with increasing age group with the majority of cases in the age group of 5–7 years. As most of the cases of ocular morbidity were preventable and treatable if detected early, emphasis on proper implementation of school eye health screening program plays a major role in reducing ocular morbidity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Ocular toxicity of daily anti-tubercular treatment regimen: A prospective observational study

ABSTRACT

Context: India carries a significant burden of TB which is the commonest cause of infectious disease-related mortality. Anti-tubercular drugs can cause serious ocular toxic effects. Optical coherence tomography (OCT) can be used as a valuable tool in the quantitative analysis of anti-tubercular treatment (ATT)-induced toxic optic neuropathy. **Aims:** To study the changes in visual parameters in patients on ATT and to analyze the OCT changes in patients by taking measurements once before initiation of treatment and once during ongoing treatment (between three and six months). **Settings and Design:** Tertiary care center, Prospective observational study. **Methods and Material:** A prospective observational study was conducted in 140 eyes of 70 subjects undergoing ATT as per the latest RNTCP guidelines where the following determinants were examined, and the corresponding values were taken once before initiation of treatment and once during ongoing treatment (between three and six months) and results were analyzed. Around 90% of the subjects were examined at the end fourth month. Visual acuity was taken using the Log Mar chart, color vision using Ishihara's chart, and slit lamp examination and fundus evaluation using a 90 D lens. OCT was done and average nasal, temporal, superior, and inferior quadrant retinal nerve fiber layer (RNFL) measurements were taken. Perimetry was also done; however, findings were not included in this study. **Statistical Analysis Used:** Frequency and percentage were applied to study the changes in visual parameters in patients on ATT. A paired *t*-test was applied for numerical variables to analyze the OCT changes in patients undergoing ATT. A P value < 0.05 was considered statistically significant. **Results:** Despite a near-normal appearance of the fundus on ophthalmoscopy, OCT clearly demonstrated and quantified the loss of retinal nerve fibers. Statistically significant RNFL thinning (P value < 0.001) was noted in the superior, temporal, and inferior quadrants and least in the nasal quadrant (P = 0.005). Significant deterioration in visual acuity was observed following three months of ATT (P = 0.001). Red-green color vision abnormalities were detected in 14 out of 140 eyes (10%). **Conclusions:** RNFL thickness was reduced on OCT. RNFL thickness quantification and assessment of other visual parameters especially color vision help in the early diagnosis of ocular toxic effects of ATT. Hence, awareness and active screening are imperative in preventing visual impairment and blindness.

Keywords: Anti-tubercular treatment, optic nerve head, optic nerve, optical coherence tomography, retinal nerve fiber layer, toxic optic neuropathies, tuberculosis

INTRODUCTION

India carries almost a quarter of the total global TB burden, and mycobacterium tuberculosis is the causative organism. Tuberculosis is an infectious disease acquired by inhalation of aerosol droplets.[1]

Due to the increasing prevalence of tuberculosis, anti-tubercular drugs are frequently used which have potential ocular side effects. Among the anti-tubercular drugs ethambutol, isoniazid (INH),

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streptomycin, kanamycin, thiacetazone, amikacin, and rifampicin are known to cause ocular toxicity. Ethambutol is a first-line drug for treating all forms of tuberculosis and is one of the major oculo-toxic agents. Exact pathophysiological mechanism leading to ocular side effects of ethambutol is still unclear. Ethambutol-induced ocular side effects can only be controlled by prompt discontinuation of the drug.[2]

The major side effect of ethambutol is optic neuritis. INH can rarely cause retro-bulbar neuritis. Central scotoma is the commonly seen visual field defect. Peripheral constriction of the visual field and abnormal color perception are also signs of toxicity. Retinal nerve fiber layer (RNFL) quantification done using optical coherence tomography (OCT) can help in the early detection of toxicity even before the appearance of fundus changes.[3]

Table 1: Color vision assessment results in samples between 3 and 6 months of ATT

Color vision	Frequency	Percentage
Normal	126	90
Abnormal	14	10
Total	140	100

Evaluation and follow-up have reported a loss of visual acuity, visual field defects, optic disc abnormalities, color vision abnormalities in eyes, and less commonly optic neuritis.[4]

INH, rifampicin, pyrazinamide, and ethambutol 4FDC (fixed drug combination) are given during the intensive phase. INH, rifampicin, and ethambutol 3 FDC are given during the continuation phase.[5]

Toxic optic neuropathy (TON) is a group of medical disorders which can be defined by visual impairment due to optic nerve damage by a toxin. Anti-tubercular treatment (ATT) induced optic neuropathy is of the toxic type.[6]

OCT is very useful in quantifying nerve fiber loss that is seen in TON.[7-10] Subclinical damage can be detected by measuring RNFL thickness.[11]

SUBJECTS AND METHODS

The study protocol was approved by the institutional ethics and research committee, and written informed consent was obtained from all participants before the enrolment

Table 2: Comparison of visual acuity before and during ATT

Time interval	*n*	Vision			Wilcoxon Signed Rank Value	*P*
		Mean	SD	Median (IQR)		
Baseline (at 0 month)	140	0.1779	0.1908	0.1800 (0.0000–0.3000)	3.276	0.001
During ATT (at 3–6 months)	140	0.1924	0.1882	0.1800 (0.0000–0.3000)		

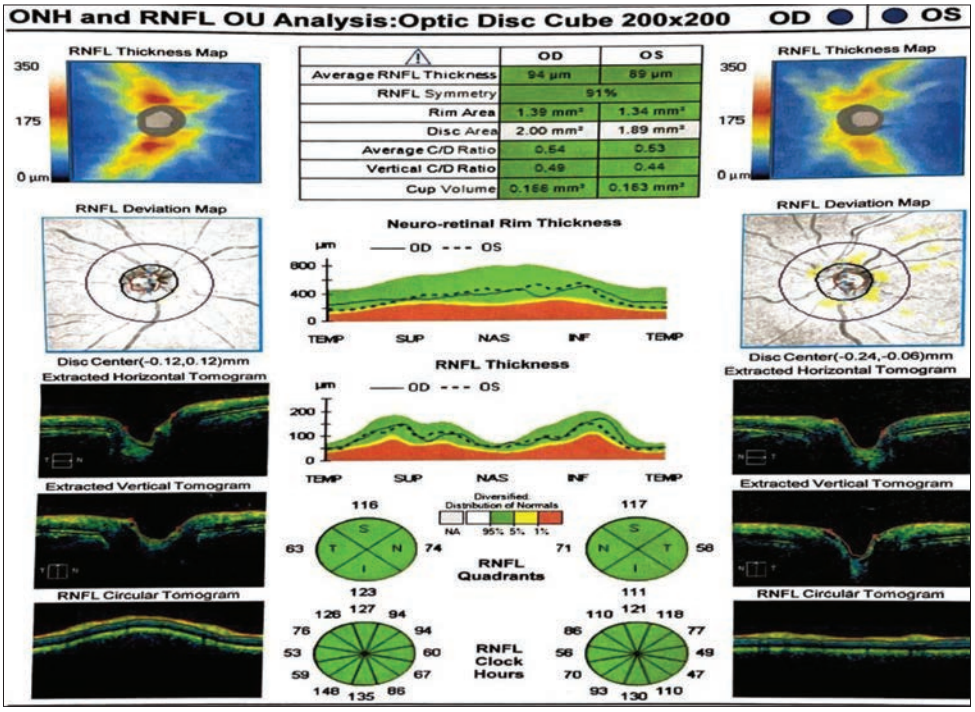


Figure 1: Normal OCT ONH – before ATT

in the study. The study period was 18 months between January 2021 and June 2022. All patients between 18 and 60 years of age group having microbiologically confirmed or clinically diagnosed active pulmonary or extra-pulmonary tuberculosis undergoing ATT as per the latest RNTCP guidelines from various departments of a tertiary health care center were studied. Patients with pre-existing optic neuropathy, retinal pathologies, glaucoma, and color vision abnormalities were excluded from the study. Anti-tubercular treatment (ATT) dropouts were also excluded from this study.

Patients were subjected to detailed ophthalmologic evaluation, including visual acuity using the Log Mar chart and color vision using Ishihara's chart. Slit lamp anterior segment evaluation, fundus evaluation using a 90D lens, and fundus photo was taken using fundus camera. Optical coherence tomography (SD-OCT, Carl-Zeiss) was done and values were recorded before the initiation of treatment [Figure 1] and anytime between three and six months during therapy [Figure 2]. RNFL thickness was measured with an optic disc cube 200 × 200 scan protocol. Best scan with signal strength >6 is used for analysis. Average nasal (NRNFL), temporal (TRNFL), superior (SRNFL), and inferior (IRNFL) quadrants RNFL measurements were noted. Through detailed clinical examination and relevant investigations, the ocular morbidity was assessed. The first examination was performed as a baseline test upon diagnosis of TB (prior to initiation of drug administration). After initiation of ATT, patients were assessed once between 3 and 6 months. Around 90% of the subjects were examined at the end fourth month. Patients were diagnosed with ocular toxicity if they have fundus changes like temporal or total disc pallor, color vision abnormalities not attributable to any other cause.

Table 3: Comparison of SRNFL thickness before and during ATT

Time interval	*n*	SRNFL		Mean difference	*t*	*P*
		Mean	SD			
Baseline (at 0 month)	140	118.38	16.26	2.71	6.27	<0.001
During ATT (at 3–6 months)	140	115.66	16.33			

Table 4: Comparison of TRNFL thickness before and during ATT

Time interval	*n*	TRNFL		Mean difference	*t*	*P*
		Mean	SD			
Baseline (at 0 month)	140	63.20	9.07	2.21	7.22	<0.001
During ATT (at 3–6 months)	140	60.99	9.98			

RESULTS

The study included a total of 140 eyes of 70 subjects having tuberculosis infection and on ATT. The mean age of the 70 study subjects included in the study was 42.43 ± 13.97 years and a maximum number of study subjects were in the 51–60 years age group (41.4%). Out of 70 subjects, 36 (51.4%) were males and 34 (48.6%) were females.

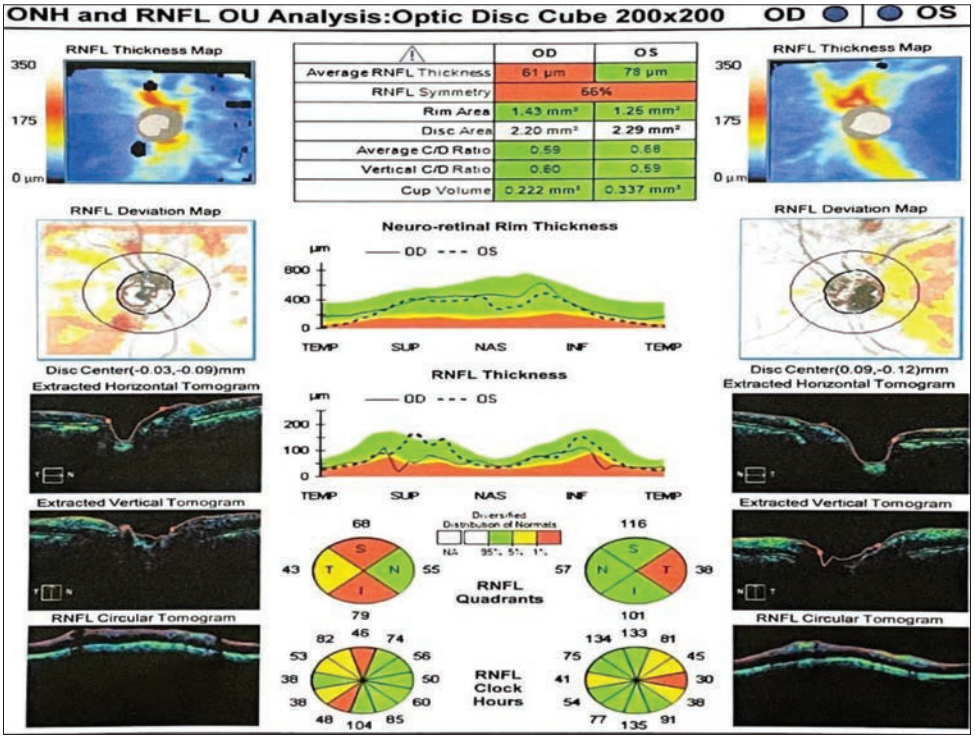


Figure 2: RNFL thinning – during ATT

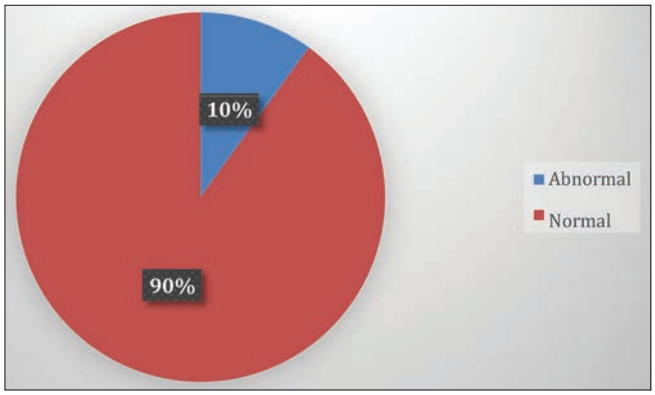


Figure 3: Color vision assessment results in samples between three and six months of ATT

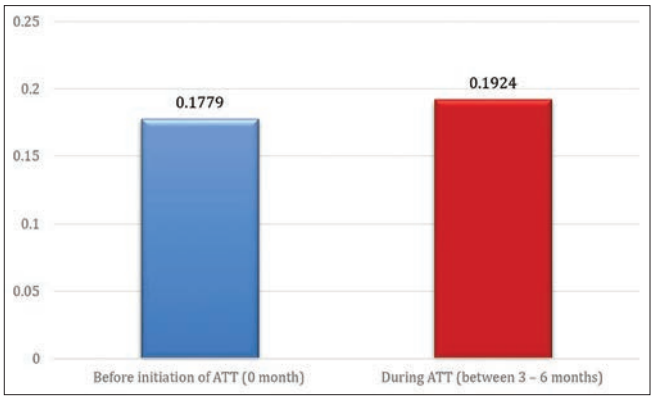


Figure 4: Comparison of visual acuity before ATT (baseline) and while on ATT

Baseline color vision was normal for all the subjects. During the 3–6 months of undergoing ATT, 14 eyes out of 140 eyes (10%) developed red-green color vision abnormalities [Table 1 and Figure 3]. The change in visual acuity was statistically significant ($P = 0.001$). Significant deterioration in visual acuity was observed during the follow-up period [Table 2 and Figure 4]. OCT clearly demonstrated and quantified the loss of retinal nerve fibers. Based on this study, among 70 study samples, statistically significant RNFL thinning (P value < 0.001) was noted in the superior [Table 3], temporal [Table 4], and inferior quadrants [Table 5]. Thinning was found to be the least in the nasal quadrant ($P = 0.005$) [Table 6].

DISCUSSION

Consumption or inhalation of various toxic agents and serious adverse drug reactions from a wide variety of agents can cause toxic optic neuropathies. Typical presentation of TON is an insidious onset of vision loss due to optic nerve damage caused by either drugs or other toxic agents. Defective vision usually happens due to retina or optic nerve damage which can cause either central or peripheral visual field involvement. Susceptibility to different agents varies from individual to individual. Differential diagnosis for TON includes compressive lesions of visual pathways, inflammatory optic neuropathies, hereditary optic neuropathies, infiltrative optic neuropathies, traumatic optic neuropathies, and nutritional optic neuropathies. Loss of central vision can also happen in bilateral occipital lesions and bilateral macular involvement. Detailed history, ophthalmic evaluation, OCT, visual fields, and necessary imaging must be done before confirming the diagnosis.[12]

An important ocular side effect following therapy is retrobulbar neuritis. Two types of retro-bulbar neuritis are usually seen.

1. The central type of retrobulbar neuritis is characterized by declining visual acuity, central scotoma, and red-green color vision defects.
2. Peripheral type, in which visual acuity may not decrease, the peripheral field of vision may narrow, and there may not be a loss of color vision.

Toxicity is usually seen following three months of ATT.[13]

Ethambutol along with other anti-tubercular drugs are commonly used for the treatment of tuberculosis. The course and outcome of ATT-induced ocular toxic effects remain unpredictable.

In our study, among 70 study subjects, only 5 subjects had complaints of defective vision during the follow-up period. Despite a near-normal appearance of the fundus on ophthalmoscopy, OCT clearly demonstrated and quantified the loss of retinal nerve fibers. Based on this study, among 70 study samples, statistically significant RNFL thinning (P value < 0.05) was noted in the superior, temporal, and inferior quadrants. Thinning was least in the nasal quadrant which signifies more nerve fiber loss in the papillomacular bundle region. Loss of retinal nerve fibers was found to be asymmetrical in most of the cases when both eyes of the same subject were compared.

When compared with the baseline visual acuity, significant deterioration in visual acuity was observed following three months of ATT, i.e., during the follow-up period ($P = 0.001$). Color vision assessment was done using Ishihara's chart and red-green color vision abnormalities were detected in 14 eyes out of 140 eyes. Identification of color plates tended to be worse in patients with significant thinning on OCT RNFL analysis, but color vision was not found to be affected in all eyes having significant thinning on OCT-RNFL analysis.

Table 5: Comparison of IRNFL thickness before and during ATT

Time interval	*n*	IRNFL		Mean difference	*t*	*P*
		Mean	SD			
Baseline (at 0 month)	140	124.18	16.61	2.71	4.74	<0.001
During ATT (at 3–6 months)	140	121.47	18.71			

Table 6: Comparison of NRNFL thickness before and during ATT

Time interval	*n*	NRNFL		Mean difference	*t*	*P*
		Mean	SD			
Baseline (at 0 month)	140	72.16	10.16	1.31	2.84	0.005
During ATT (at 3–6 months)	140	70.85	11.59			

Aziz Gümüş *et al*.[8] in a study reported thinning in RNFL after the two-month treatment period compared to baseline values. Patients receiving these drugs can be followed via OCT in terms of reduction in RNFL thicknesses for early diagnosis of toxicity. Compared to baseline values, after the two-month treatment period, thinning was detected in the right eye's average and superior quadrant RNFLs ($P = 0.024$ and $P = 0.006$, respectively) and in the left eye's average, superior quadrant, and inferior quadrant RNFLs ($P = 0.001$, $P = 0.008$, $P < 0.001$, respectively). In our study subjects OCT RNFL thinning was seen in superior, temporal, and inferior quadrants (P value < 0.05).

Yong-Kyu Kim *et al*.[9] in a study concluded that OCT may be helpful for the follow-up of patients with TON.

In our study OCT changes preceded fundus changes, so OCT may be useful in early detection, follow-up and management of toxic optic neuropathies.

In a study done by S M Konnakkodan *et al*.[10] out of 40 eyes receiving ethambutol at a mean daily dose of 17.61 ± 1.73 mg/kg/day, color vision was defective in 35 eyes while in our study red-green color vision abnormalities were observed in 10% of the study subjects following ATT. ONH-RNFL thickness was reduced on SD-OCT which helps to quantify the role of various risk factors in EMB toxicity, making it a useful tool for objective assessment. Awareness and active screening for the detection of early toxicity are needed to prevent vision loss.

Optic nerve head remains normal on ophthalmoscopic examination until late in the disease. Clinical examination findings become apparent only when pallor sets in. Improvement in visual acuity usually happens only in a minority of patients following discontinuation of the drug. So, ophthalmic evaluation has to be done in all patients undergoing ATT.[14]

The limitation of the study is that electrophysiological studies could not be done due to limited resources. Further studies based on visual evoked potential can help in addition to OCT for the detection of ATT-induced optic neuropathies.

CONCLUSION

Our findings suggest that since RNFL thinning can be detected before the appearance of clinical symptoms and fundus changes, OCT can help in early detection, follow-up, management, and can help in preventing permanent visual damage. Color vision defects were also seen in some subjects with RNFL thinning on OCT. The treatment of ocular toxic effects due to ATT is mainly by early detection and by stopping the offensive drug. It is imperative to create awareness about the ocular toxic effects of anti-tubercular drugs so that periodic ophthalmological screening can be done in patients undergoing ATT.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Systemic risk factors for diabetic retinopathy in patients with type 2 diabetes mellitus- A cross-sectional study in a South Indian cohort

ABSTRACT

Purpose: Diabetic retinopathy (DR) is a multifactorial disease. The objective of the current study was to evaluate the systemic risk factors for diabetic retinopathy in patients with type 2 DM in a South Indian Cohort. **Materials and Methods:** ***Design:*** Cross-sectional analytical. All participants fulfilling the eligibility criteria were recruited into two groups: with DR (Group 1) and without DR (Group 2). Both groups were compared for the risk factors using univariate and logistic regression analysis and adjusted Odds ratios (OR) were calculated. Patients in Group 1 were further divided into subgroups based on severity of DR and risk factors were analysed across the subgroups. **Results:** 93 patients were recruited in each group. Comparing Group 1 versus Group 2: On logistic regression analysis, factors like HbA1c >8% (adjusted OR 7.1), duration >10 years (adjusted OR 22.15), insulin treatment (adjusted OR 6.34), CKD (adjusted OR 12.18), and hypertension (adjusted OR 8.22) were associated with presence of any stage DR. Comparing risk factors across Group 1: HTN and insulin treatment were associated with severity of DR. **Conclusion:** Insulin treatment for type 2 DM was found to be an additional risk factor in our study. However, this finding needs to be further validated in future prospective cohort studies on larger sample sizes.

Keywords: Diabetic retinopathy, glycaemic control, glycated hemoglobin, hypertension, type 2 diabetes mellitus

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of blindness in working-age adults with type 2 diabetes mellitus (DM). Approximately one-third of patients with DM worldwide show some evidence of DR on fundus examination, and one-third of these may present with sight-threatening DR (STDR).[1,2] Hyperglycaemia, hypertension (HTN), and the duration of diabetes are the most important risk factors associated with the development and progression of DR; however, these factors alone cannot always explain the risk of development of DR.[3] DR is, in fact, a multifactorial disease. Pro-inflammatory mediators, angiogenesis mediators, chronic inflammation, and oxidative stress- all play significant roles in the pathogenesis of the disease.[4,5] Hyperglycaemia and HTN have shown strong associations with DR in various studies, albeit with considerable variations in the consistency, strength, and pattern of the associations. DM duration has also been established as a major factor associated with DR. Similarly, microalbuminuria has been reported to be a marker for DR and other microvascular dysfunctions.[4,6-15] All these factors have also been reported to show regional and ethnic variations.[1] Developing an accurate estimate of DR in terms of its prevalence and its association with the major risk factors is pivotal for effective management of DR, especially sight-threatening DR.[8] The objective of our study was, therefore, to evaluate the systemic risk factors

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for diabetic retinopathy in patients with type 2 DM in an ethnically diverse south Indian cohort. The primary outcome was a comparison of the risk factors associated with Diabetic retinopathy for two groups- DR present versus DR absent. The secondary outcome was evaluation of the risk factors associated with the severity of Diabetic retinopathy (Mild to moderate Non- proliferative DR-NPDR versus severe/very severe NPDR versus Proliferative DR and advanced diabetic eye disease-ADED).

MATERIALS AND METHODS

This is a cross-sectional analytical study conducted in the Department of ophthalmology in a tertiary institute in south India between June 2018 and June 2020. The study approval was obtained from the institutional ethics committee (IEC) (approval number: JIP/IEC/2018/454), and it adhered to the tenets of the declaration of Helsinki. Written informed consent was taken from all the patients. All participants were enrolled based on the inclusion and exclusion criteria.

Inclusion criteria

Any patient with type 2 diabetes mellitus attending the ophthalmology out patient department (OPD) during the study period.

Exclusion criteria

Patients with lens and corneal opacities precluding visualization of the fundus.

Any intraocular surgery in the last three months.

Suspected narrow-angle glaucoma.

Patients with associated immunological disorders.

Patients on systemic steroids.

Sample size calculation

The sample size was determined using the sample size estimation formula for comparing two means.[16] Glycated hemoglobin (HbA1C) level was considered the most important predictor for diabetic retinopathy risk for sample size estimation. The minimum expected difference in the means between the groups was considered to be 0.66.[17] The estimated sample size was 92 in each group at a 5% level of significance and 80% power. The sample size was calculated using the power and sample size calculator software.

Study procedure

All patients with type 2 DM attending the Ophthalmology OPD were screened for diabetic retinopathy (DR). Demographic data and other details like duration of diabetes, anti-diabetic medications, HTN, chronic kidney disease (CKD), etc., were noted. The screening was done by dilated fundus evaluation with slit-lamp bio-microscopy and indirect ophthalmoscopy by trained ophthalmologists. Fundus photo was taken for all patients with DR changes. Early treatment diabetic retinopathy scale (ETDRS) classification was used to grade DR. Patients screened for diabetic retinopathy (DR) were categorized into two groups: Group 1: DR present (DR in one eye or both eyes), Group 2: DR absent. The patients in Group 1 were further divided into very mild, mild, moderate, severe, and very severe Non-Proliferative Diabetic Retinopathy (NPDR), Proliferative Diabetic Retinopathy (PDR) and Advanced Diabetic Eye Disease (ADED). In case both the eyes in a patient had DR changes, the patient was sub-grouped based on the higher DR stage.

Laboratory investigations for all patients included fasting blood sugar (FBS), post-prandial blood sugar (PPBS), glycated hemoglobin (HbA1C), fasting lipid profile, hemoglobin, urine albumin, blood urea, and serum creatinine. Best-corrected visual acuity (BCVA) and refraction were done for all patients. Optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) were done whenever indicated based on the stage of DR and DME. All the data collected were finally analyzed for the study variables.

The body mass index (BMI) was calculated using the formulae: BMI = (weight in kg)/(height in m2). The target for glycaemic control was considered as glycated hemoglobin less than or equal to 7%. Hypertension was set as blood pressure greater than or equal to 140/90 mmHg or the use of any antihypertensive therapy. Dyslipidemia was set as triglycerides greater or equal to 150 mg/dl and total cholesterol ≥200 mg/dL or use of statins for dyslipidemia. Diabetic nephropathy (or CKD) was set as microalbuminuria 30–300 mg/L, macroalbuminuria >300 mg/L or previous diagnosis of disease.[4,18]

Statistical analysis

The association of factors with DR among the patients with DM was established using the Chi-square test. The continuous variables were compared between patients with and without DR using an independent sample *t*-test or Mann-Whitney test depending on the normality of the variables. Similarly, a comparison between various categorical variables of very mild/mild/moderate non-proliferative DR (NPDR) versus severe/very severe non proliferative DR versus proliferative DR (PDR)/advanced diabetic eye disease (ADED) was made

using the Chi-square test. Comparison between various continuous variables and the presence of PDR vs. NPDR was made using an independent sample *t*-test or Mann-Whitney test depending on the normality of the independent variables. A multicollinearity diagnosis was performed. Logistic regression analysis was done for the significant factors, and an adjusted odds ratio (OR) was calculated. All the tests were carried out at a 5% level of significance, and data were analyzed using the IBM-SPSS program (SPSS version 20.0); SPSS Inc, Chicago, IL.

RESULTS

A total of 186 participants were enrolled for the study - 93 patients with diabetic retinopathy (Group 1) and 93 patients without diabetic retinopathy (Group 2). Baseline demographic features and DR grading for the participants are shown in Table 1. A comparison of the risk factors across Group 1 versus Group 2 is shown in Table 2. Table 3 shows a comparison of various risk factors across patients in Group 1 based on the severity of DR. Table 4 shows logistic regression analysis for the risk factors for DR.

Age

The mean age of all the study participants was 55.3 (±10.5) years- 58.7 years in Group 1 and 51.9 years in Group 2. Increasing age was found to be associated with the development of DR (OR 1.07, $P < 0.001$) on univariate analysis. Logistic regression, however, did not show any association of DR with increasing age (Adjusted OR 1.02, $P = 0.422$).

Gender

95 (51.1%) participants were females, while 91 (48.9%) participants were males. No significant association was noted between gender and development of DR on comparison between the two groups [Table 2].

Duration of DM

In comparison between group 1 and group 2, patients with a longer duration of DM had a higher chance of development of DR ($P < 0.001$) on univariate analysis [Table 2]. On further logistic regression analysis also, the duration of DM above ten years was found to be associated with DR development (adjusted Odds ratio of 22.15, $P < 0.001$) [Table 4]. However, on comparing patients

Table 1: Socio-demographic characteristics and diabetic retinopathy status of the study population (*n*=186)

Characteristics	Frequency (%)		
Age distribution			
34 – 45 years	40 (21.5%)		
46-60 years	92 (49.5%)		
61 – 70 years	40 (21.5%)		
71 – 80 years	14 (7.5%)		
Mean (SD) age in years	55.3 (10.5)		
Gender distribution			
Males	91 (48.9%)		
Females	95 (51.1%)		
Duration of diabetes			
Less than 2 years	49 (26.3%)		
2 – 5 years	51 (27.4%)		
5 – 10 years	50 (26.9%)		
11 – 25 years	36 (19.4%)		
	Diabetic Retinopathy status		
	Right eye	Left eye	Total eyes
NO DR (Control Group 2): 93 patients and 186 eyes	93 (50%)	93 (50%)	186
DR present (Group 1): 93 patients and 186 eyes	93	93	186
Very Mild NPDR	7 (3.7%)	4 (2.1%)	11 (5.91%)
Mild NPDR	17 (9.1%)	25 (13.4%)	42 (22.58%)
Moderate NPDR	24 (12.9%)	21 (11.3%)	45 (24.19%)
Severe NPDR	16 (8.6%)	15 (8.1%)	31 (16.66%)
Very Severe NPDR	4 (2.2%)	3 (1.6%)	7 (3.76%)
Early Proliferative DR	8 (4.3%)	8 (4.3%)	16 (8.60%)
High Risk Proliferative DR	17 (9.1%)	14 (7.5%)	31 (16.66%)
Advanced Diabetic Eye Disease	0	3 (3.2%)	3 (1.6%)
CSME in eyes with DR	50 (53.1%)	54 (58.06%)	104/186 (55.9%)

DR=Diabetic retinopathy, NPDR=Non-proliferative DR, PDR=Proliferative DR. CSME=Clinically significant macular edema

Table 2: Comparison of risk factors across patients with (group 1) and without diabetic retinopathy (group 2)

Risk factors	Diabetic retinopathy (Group 1) (*n*=93)	No Diabetic retinopathy (Group 2) (*n*=93)	*P*
Gender distribution			
Males	50 (53.8%)	41 (44.1%)	0.187
Females	43 (46.2%)	52 (55.9%)	
Duration of diabetes			
Less than 2 years	13 (14.0%)	36 (38.7%)	<0.001*
2 – 5 years	24 (25.8%)	27 (29.0%)	
5 – 10 years	28 (30.1%)	22 (23.7%)	
11 – 25 years	28 (30.1%)	8 (8.6%)	
BMI category			
Less than 18.5 (underweight)	5 (5.4%)	1 (1.1%)	0.144
18.5 – 22.9 (normal)	64 (68.8%)	71 (76.3%)	
23 – 24.9 (overweight)	16 (17.2%)	18 (19.4%)	
More than 25.0 (obese)	8 (8.6%)	3 (3.2%)	
Anemia			
Anemic	60 (64.5%)	51 (54.8%)	0.179
Normal	33 (35.5%)	42 (45.2%)	
Fasting Blood glucose levels			
High	85 (91.4%)	75 (80.7%)	0.034*
Normal	8 (8.6%)	18 (19.3%)	
Post prandial Blood glucose levels			
High	89 (95.7%)	72 (77.4%)	<0.001*
Normal	4 (4.3%)	21 (22.6%)	
HbA1c			
Normal (<6%)	5 (5.4%)	21 (23.6%)	<0.001*
Good control (6.1 to 7%)	6 (6.5%)	35 (39.3%)	
Fair control (7.1 to 8%)	12 (13.0%)	16 (18.0%)	
Poor control (>8%)	69 (75.0%)	17 (19.1%)	
Triglyceride			
Abnormal	36 (38.7%)	22 (23.7%)	0.027*
Normal	57 (61.3%)	71 (76.3%)	
LDL cholesterol			
Abnormal	29 (31.2%)	29 (31.2%)	1.000
Normal	64 (68.8%)	64 (68.8%)	
HDL Cholesterol			
Abnormal	54 (58.1%)	54 (58.1%)	1.000
Normal	39 (41.9%)	39 (41.9%)	
Urea			
Abnormal	25 (26.9%)	3 (3.2%)	<0.001*
Normal	68 (73.1%)	90 (96.8%)	
Creatinine			
Abnormal	25 (26.9%)	5 (5.4%)	<0.001*
Normal	68 (73.1%)	88 (94.6%)	
CKD status			
CKD present	22 (23.6%)	2 (2.1%)	<0.001*
No CKD	71 (76.4%)	91 (97.9%)	
Hypertension status			
Hypertensive	66 (71.0%)	16 (17.2%)	<0.001*
No hypertension	27 (29.0%)	77 (82.8%)	
Treatment			
Oral drugs	53 (57.6%)	91 (97.8%)	<0.001*
Insulin	39 (42.4%)	2 (2.1%)	

with very mild/mild/moderate NPDR versus Severe/very Severe NPDR versus PDR/ADED, no significant association was found between DR severity and duration of DM ($P = 0.593$) [Table 3].

Table 3: Comparison of risk factors across patients with very mild/mild/moderate non-proliferative versus Severe/Very severe non proliferative versus proliferative or advanced diabetic retinopathy in group 1

Duration of diabetes	Very mild/mild NPDR/ Moderate NPDR (*n*=48)	Severe/Very severe Non-Proliferative Diabetic Retinopathy (*n*=19)	Proliferative Diabetic Retinopathy and ADED (*n*=26)	*P*
Less than 2 years	8 (16.6%)	1 (5.2%)	4 (15.4%)	0.593
2 – 5 years	13 (27.1%)	6 (31.5%)	5 (19.2%)	
5 – 10 years	16 (33.3%)	4 (21.0%)	8 (30.8%)	
11 – 25 years	11 (22.9%)	8 (42.1%)	9 (34.6%)	
Anemia				
Anemic	26 (54.2%)	13 (68.4%)	21 (80.8%)	0.068
Normal	22 (45.8%)	6 (31.6)%	5 (19.2%)	
Fasting Blood glucose levels				
High	45 (93.7%)	18 (94.7%)	22 (84.6%)	0.345
Normal	3 (6.3%)	1 (5.3%)	4 (15.4%)	
Post-prandial Blood glucose levels				
High	47 (97.9%)	18 (94.7%)	24 (92.3%)	0.511
Normal	1 (2.1%)	1 (5.3%)	2 (7.7%)	
HbA1c				
Normal (<6%)	4 (8.3%)	0	1 (3.8%)	0.189
Good control (6.1 to 7%)	1 (2.1%)	1 (5.3%)	4 (15.4%)	
Fair control (7.1 to 8%)	8 (16.7%)	1 (5.3%)	3 (11.5%)	
Poor control (>8%)	34 (70.8%)	17 (89.5)%)	18 (69.2%)	
Hypertension status				
Hypertensive	31 (64.6%)	11 (57.9%)	24 (92.3%)	0.016*
No Hypertension	17 (35.4%)	8 (42.1%)	2 (7.7%)	
Treatment				
Oral drugs	35 (72.9%)	10 (52.6%)	8 (32.0%)	0.003*
Insulin	13 (27.1)	9 (47.4%)	17 (68.0%)	

Table 4: Logistic regression to identify risk factors for diabetic retinopathy

Factors	Unadjusted OR	*P*	Adjusted OR	*P*
Age (one unit increase)	1.07 (1.03 – 1.10)	<0.001	1.02 (0.96 – 1.08)	0.422
HbA1c category				
Normal (<6%)	Ref		Ref	
Good control (6.1 to 7%)	0.72 (0.19 – 2.65)	0.622	1.16 (0.19 – 7.04)	0.870
Fair control (7.1 to 8%)	3.15 (0.92 – 10.77)	0.067	4.82 (0.75 – 30.89)	0.097
Poor control (>8%)	17.04 (5.61 – 51.74)	<0.001	37.1 (5.93 – 232.7)	<0.001
Abnormal Triglyceride	2.03 (1.08 – 3.84)	0.028	0.53 (0.17 – 1.68)	0.284
CKD present	14.09 (3.20 – 61.96)	<0.001	12.18 (1.35 – 109.46)	0.026
Hypertension present	11.76 (5.83 – 23.69)	<0.001	8.22 (2.94 – 22.93)	<0.001
Insulin treatment	33.48 (7.76 – 144.28)	<0.001	6.34 (1.08 – 37.04)	0.040
Duration of diabetes				
Less than 2 years	Ref	-	Ref	-
2 – 5 years	2.46 (1.06 – 5.69)	0.035	1.75 (0.34 – 8.97)	0.502
5 – 10 years	3.52 (1.51 – 8.20)	0.003	5.38 (0.90 – 32.11)	0.064
11 – 25 years	9.69 (3.53 – 26.6)	<0.001	22.15 (2.50 – 195.94)	0.001

Body mass index (BMI)

No significant association was established between BMI and the development of DR ($P = 0.144$) [Table 2] on comparison between Group 1 and Group 2.

Anaemia

There was no significant association noted between anemia and development of DR [Table 2] on comparison between the two groups. There was also no significant association with anemia and severity of DR ($P = 0.068$) [Table 3].

Fasting and post-prandial blood glucose levels

Both higher fasting ($P = 0.034$) and post-prandial blood glucose levels had significant associations with the development of DR ($P < 0.001$) [Table 2]. However, there was no relation between the blood glucose levels with the severity of DR [Table 3].

Glycated hemoglobin (HbA1c) levels

There was a greater risk of DR development in patients with higher levels of HbA1c ($P < 0.001$) [Table 2] on comparison between group 1 and group 2. However, HbA1C level was not associated with the severity of DR [Table 3] on comparison between very mild/mild/moderate NPDR versus severe/very severe NPDR versus PDR/ADED. In logistic regression analysis, poor HbA1c control (>8%) had a higher risk of DR onset (OR = 37.1, $P < 0.001$) [Table 4].

Dyslipidemia

No significant associations were noted between the serum HDL and LDL levels with DR development [Table 2]. Serum triglyceride levels had a significant association with DR development on univariate analysis of the inter-group comparison [Table 2]. However, logistic regression analysis did not show any association between serum triglyceride levels and DR development [Table 4].

Chronic kidney disease (CKD)

On comparing group 1 and group 2, patients with CKD were found to have a higher risk of developing DR on both univariate analysis [Table 2] and logistic regression analysis [Table 4]. Blood urea and creatinine levels also had significant associations with DR development ($P < 0.001$) [Table 2] on univariate analysis.

Hypertension

On comparing both the groups, significant associations were found between HTN and DR development in both univariate analysis [Table 2] and logistic regression analysis [Table 4]. There is also a significant association between the severity of DR and presence of HTN ($P = 0.016$). [Table 3].

Treatment of DM

In our study, we found statistically significant associations between insulin treatment and risk of development as well as the progression of DR on both univariate analysis [Table 2] and logistic regression analysis [Table 4]. There is also a significant association between the severity of DR and the treatment of DM with Insulin ($P = 0.003$) [Table 3].

Therefore, on comparing both the groups using univariate analysis, the risk factors that were significantly associated with DR development were age, FBG, PBG, HbA1c, triglycerides, blood urea, serum creatinine, chronic kidney disease, duration of diabetes, insulin treatment, and hypertension. The multicollinearity diagnosis was performed, which excluded FBG, PBG (high collinearity with HbA1c), blood urea, and serum creatinine (high collinearity with CKD status). Logistic regression analysis with adjusted odds ratio (OR) was performed subsequently [Table 4]. After the regression analysis, the factors which were significantly associated with the development of DR were poor glycaemic control (HbA1c), duration of diabetes, insulin treatment, CKD, and hypertension, albeit with a wide confidence interval.

DISCUSSION

There are few similar cross-sectional and retrospective studies on Indian cohorts available in the literature.[11-15] The progression of DR is influenced by various risk factors that affect the onset and progression of DR - modifiable and non-modifiable risk factors.[14,19] In our study, we determined the association between these risk factors and the development of DR as well as its severity.

Gender had no association with DR development in our study. Age, on the other hand, showed an association with DR development in univariate analysis. However, on logistic regression analysis, the odds for DR lost statistical significance. Similar results of no association between DR and age or gender have been reported previously in the literature[4,17,20,21] There are also few studies that report the association of DR with either the male gender[7,22] or female gender.[23] The UK prospective diabetes study (UKPDS) reported that the relative risk for progression of DR was lower in women.[24] In another study, a greater chance of DR development was seen in the age groups of 50-59 years and >60 years.[25]

Duration of DM is an important predictor of the development of DR.[26-30] It was also found to be an independent risk factor for the development of sight-threatening DR.[31] In our study, a comparison of group 1 versus group 2 showed a strong association between the duration of diabetes and the development of diabetic retinopathy on both univariate and logistic regression analyses. An adjusted odds ratio of 22.15 ($P < 0.001$) was found for the presence of DR in patients with a duration of DM above ten years. However, there was no association between the duration of DM and the severity of DR. In a similar case-control study by Lima *et al*.,[4] a high association with DR was reported after ten years duration of DM. In the study by Al-Sarraf *et al*.,[25] the association was found to be two times for >10 years DM duration, which further increased to three times for disease duration >20 years. Disease duration is probably the most important independent risk factor for DR, as also evident from a high adjusted odds ratio (22.5) in our study.

HbA1c is one of the most important risk factors for the development and progression of DR. UKPDS has reported that patients with HbA1c <7% had a lower risk of development of

DR.[24] The intense control group (HbA1c <6%) in the action to control cardiovascular risk in diabetes (ACCORD) eye study showed a 33% reduction in the progression of DR.[32] In the action in diabetes and vascular disease: reterax and diamicron modified release controlled evaluation (ADVANCE) trial,[33] tight glycaemic control (HbA1c <6.5) did not affect retinopathy development or progression. According to the SPEED study,[15] there was a 2-fold increased risk of retinopathy in patients with poor glycaemic control. Other studies like the CURES study and the DIAMOND study also reported an increase in the prevalence of DR with an increase in glycated hemoglobin levels.[13,14] Similarly, in our study on comparing both groups using univariate and logistic regression analyses, we found a significant association between HbA1c and the onset of DR. In regression analysis, it was found that patients with poor control of HbA1c (>8%) had a higher risk of DR with an adjusted OR of 37.1.

In our study, elevated serum triglycerides had a significant association with the development of DR on univariate analysis, which, however, was subsequently noted to be insignificant on logistic regression analysis. The Beijing eye study found no association between increased cholesterol levels and DR.[34] A study by Lima *et al*.[4] also reported no significant association between dyslipidemia and DR. The CURES study, on the contrary, reported a significant association of serum triglycerides with DR and low-density lipoprotein with diabetic macular edema.[13]

Hypertension is one of the most important risk factors for the development of DR, as reported in various studies.[17,21] However, the study by Lima *et al*.[4] had reported that hypertension was not an independent risk factor for DR. In our study, co-existent HTN had higher odds of DR development as well as the occurrence of severe stages of DR on comparing both the groups using univariate and logistic regression analyses.

Renal dysfunction is a risk factor for the progression and worsening of diabetic retinopathy.[35] A study by Tamadon *et al*.[36] reported a significant association between blood urea and development as well as the severity of DR, but no significant association between serum creatinine and development of DR. In a study by Almutairi *et al*.,[37] serum creatinine levels and the onset of DR were reported to have no significant association. In another cohort study in China, it was found that patients with higher serum creatinine values had a higher risk of developing proliferative diabetic retinopathy.[38] Blood urea and creatinine levels, and CKD status- all had significant associations with the development of DR as well as the severity of DR in our study on univariate analysis. After multicollinearity diagnosis and exclusion of urea and creatinine levels, CKD status was found to have a significant association with DR even on logistic regression analysis.

BMI and anemia both were noted to have no direct relationship with DR development in our study. Few prior studies have shown a high association between DR and these factors, while few others have shown contradictory results.[11,39-41] Nevertheless, the importance of these factors cannot be underestimated in the management of DM.

Concerning treatment for DM, we found by comparing group 1 versus group 2 that patients on insulin had higher odds of developing any stage of DR on both univariate and logistic regression analyses. Insulin therapy was also associated with more severe stages of DR. A study by Gunnlaugsdottir *et al*.[9] had shown similar results. Patients on insulin therapy were at higher risk for the development of any stage of DR as well as more severe stages of DR. A study by Lima *et al*.[4] found a significant association between insulin therapy and the chance of DR in bivariate analysis, but this association lost significance in multivariate analysis. Liu Yang *et al*.[31] in another study, reported that there was no significant association between insulin treatment and the development of DR. Studies on the association between insulin therapy and DR in type 2 DM, therefore, provide contradictory results.

Hyperglycaemia, DM duration, HTN, and CKD are well-established risk factors of DR, which corroborates well with our study findings. In the current study, however, we found insulin treatment in type 2 DM to be an additional significant risk factor for DR, which is quite interesting. Insulin treatment was also associated with the severity of DR. In a meta-analysis done by Zhao *et al*.,[42] a significant association was found between insulin therapy and DR. On adjusting for DM duration, the significance of this association was, however, lost. On the contrary, the strength of the association in our study was maintained after adjustment for other confounding variables. The mechanism underlying this paradoxical worsening of retinopathy with insulin therapy is not clear. The synergistic action of exogenous insulin with vascular endothelial growth factor (VEGF) in triggering vascular proliferation is the most accepted theory.[43] Patients on insulin should, therefore, be more carefully evaluated for DR detection and also closely followed up for progression of DR.[42]

One limitation of the study is that DR was diagnosed and classified based on clinical fundus examination by trained

ophthalmologists. There is a possibility of inter-observer variation in the diagnosis and classification of DR. Fundus photography graded by two or more certified graders would be a robust way of detecting DR and its severity. Wide-field retinal imaging is also a very sensitive tool and may be able to diagnose cases with early stages of NPDR or PDR, which was beyond the scope of our study.[4] Another limitation is the wide confidence interval obtained on logistic regression in our study. This may be due to a smaller sample size while doing subgroup analysis. Therefore, the conclusions drawn from the data need to be replicated with a larger sample size.

CONCLUSION

Mechanisms for the development and progression of diabetic retinopathy are not fully elucidated. The current study highlights the impact of various risk factors on the development as well the severity of DR. Successful management of DM, therefore, requires effective screening and treatment of all associated DR risk factors. According to the results of our study, patients with poor glycaemic control, longer duration of diabetes, CKD, and hypertension are at a greater risk of developing diabetic retinopathy. These findings are in concordance with the results of prior studies.[8-15] Insulin therapy was found to be an additional significant risk factor for DR in type 2 DM. HTN and insulin treatment were also found to be associated with the severity of DR when risk factors were analyzed across patients with DR. However, this finding needs to be validated further in future prospective cohort studies on larger sample sizes.

Ethics approval

The study was approved by the institute's ethics committee and it was conducted in accordance with the ethical standards of 1964 Helsinki declaration and its later amendments.

Consent to participate

Our study involves human participants. Informed consent was obtained from all.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Posterior segment optical coherence tomography: A diagnostic aid in posterior uveitis

ABSTRACT

Background: Patients with posterior uveitis can develop vision-threatening complications. Optical coherence tomography (OCT) plays an important role in the diagnosis and management of these complications. **Aims:** The objectives of this study were to describe different retinal morphological characteristics presenting on OCT in patients with posterior uveitis, with an aim to facilitate early diagnosis to initiate specific treatment and also to observe the response to treatment. **Materials and Methods:** A cross-sectional prospective non-randomized study was undertaken at a tertiary eye care hospital. The study included 30 eyes of 30 patients with posterior uveitis between the period of May 2016 and May 2018. All subjects underwent a set of systemic investigations for etiological diagnosis and complete ophthalmic examination, including OCT (Zeiss Cirrus machine (model number 5000)] imaging). Data were collected and analyzed. A *P* value of <0.05 was considered statistically significant. **Results:** The mean patient age was 33.1 ± 4.2 years. Infectious etiology was diagnosed in 13 patients (43.33%) of which toxoplasma chorioretinitis (36.66%) was the most common infection. Among 17 patients with noninfectious uveitis (56.66%), Vogt-Koyanagi-Harada (VKH) disease and multifocal choroiditis (16.67% each) were the most common causes. RPE-Bruch's membrane abnormalities were seen in 96.67% of patients. Subretinal detachment (26.67%) was the most common type of macular edema on OCT. Significant differences in central foveal thickness posttreatment were noted in cases with VKH syndrome and toxoplasma retinochoroiditis ($P < 0.05$). **Conclusion:** OCT is a useful tool complementary to conventional fundus photography and fluorescein angiography in patients with posterior uveitis.

Keywords: Posterior segment optical coherence tomography, posterior uveitis, retinal complications

INTRODUCTION

Uveitis represents a major cause of ocular morbidity worldwide.[1] More than half of all patients with uveitis develop sight-threatening complications related to their disease, and up to 35% suffer severe visual impairment.[1,2] Uveitis and its complications are responsible for 5%–10% of all causes of legal blindness in developed countries.[3] There can be numerous causes of uveitis, including infectious conditions, autoimmune diseases, trauma, and tumors.[4]

Patients with posterior uveitis can develop complications, including macular edema, epiretinal membrane, vasculitis, retinal arterial and venous occlusions, retinal necrosis, tractional retinal detachment, choroidal or retinal neovascularization, and vitreal or intraretinal bleeding.[5] Fluorescein angiography (FA), indocyanine green angiography, OCT, and ultrasound play an important role in the diagnosis and management of posterior uveitis.[6,7] FA was used for a long time as the primary imaging modality to detect macular edema, choroidal neovascularization, and serous retinal detachment.[7] Apart from being an invasive diagnostic modality, it does not provide any three-dimensional anatomic information about the retinal layers, the retinal pigment epithelium, or the choroid. The advent of OCT has made it possible to have high-resolution cross-sectional images of the retina, shedding light on the pathophysiology of several posterior uveitic entities.[6,8]

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This study was undertaken with the objectives of describing different retinal morphological characteristics that can present on OCT in cases with posterior uveitis, facilitating early diagnosis, initiating specific treatment, and monitoring the response to treatment.

MATERIALS AND METHODS

A cross-sectional prospective non-randomized study was undertaken at our hospital from May 2016 to May 2018. The study was approved by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients before the start of the study. All the patients diagnosed as having posterior uveitis attending the vitreo retinal clinic of our institute were included in the study.

Patients with a history of ocular trauma, concurrent ocular pathology, associated anterior uveitis and those with vitritis where media was not sufficiently clear to obtain reliable OCT images were excluded.

A detailed history of each patient including systemic illness was taken. All subjects underwent a complete ocular examination including visual acuity, anterior segment evaluation, 90 D slit lamp biomicroscopy, binocular indirect ophthalmoscopy, and optical coherence tomography (OCT) [Zeiss Cirrus machine (model number 5000)] imaging. We did only macular OCT scan to evaluate premacular vitreous, macula, and choroid. Scans through peripheral retinal lesions were not performed. Investigations carried out for systemic evaluation included:

1. Routine blood investigations like complete blood count, erythrocyte sedimentation rate, blood glucose level, and renal and liver function tests.
2. Disease-specific laboratory investigations like human immunodeficiency virus, hepatitis B surface antigen, serum angiotensin converting enzyme, Mantoux test, veneral disease research laboratory tests, toxoplasma Ig G and Ig M antibodies, and rheumatoid arthritis factor.
3. Radiological investigations like x-ray imaging of chest and sacroiliac joints.

   OCT images were taken before starting treatment and posttreatment in the 1st, 6th, and 12th week. Pre- and posttreatment images were compared and taken into statistical analysis. The patient was advised to consult the concerned medical specialist whenever needed for pharmacological treatment. Systemic steroids (1 mg/kg body wt./day) were also started if not contraindicated.

Data were analyzed using Microsoft Excel 2019 and SPSS (version 20, SPSS Inc., Chicago, US). Nominal variables were described using frequencies and percentages, while continuous variables were described by the mean and standard deviation. The Kolmogorov–Smirnov test was performed in order to analyze the normal distribution of the variables. The independent samples test was used for intergroup comparisons of parameters. *P* value was calculated for posttreatment reduction in central foveal thickness (CFT) and posttreatment visual improvement. A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 30 patients (14 males and 16 females) who were diagnosed with posterior uveitis were enrolled in the study. The mean patient age was 33.1 ± 4.2 years (range: 13–65 years). Infectious etiology was diagnosed in 13 patients (43.33%), of which toxoplasma chorioretinitis (36.66%) was the most common infection.

Among patients with noninfectious uveitis ($n = 17$) (56.66%), Vogt-Koyanagi-Harada (VKH) disease and multifocal choroiditis (16.67% each) were the most common causes [Table 1].

On subjecting patients to posterior segment OCT before starting treatment, vitreoretinal interface disturbances were seen in 15 patients (50%), distortion of foveal contour in 14 patients (46.47%), disturbed intraretinal architecture in 26 patients (86.67%), and RPE-Bruch's membrane abnormalities in 29 patients (96.67%).

The most common type of macular edema was subretinal detachment ($n = 8$) (26.67%), followed by diffuse spongy edema ($n = 7$) (23.33%). Cystoid edema was observed in five cases (16.66%) and cystic spongy in six cases (20%). Four patients (13.33%) had a normal macula.

The role of macular OCT in the diagnosis of etiological conditions of posterior uveitis is described in Table 2. OCT

Table 1: Etiological classification of uveitis

Etiology and No. of patients (*n*)	Percentage of total cases
Infectious Causes ($n=13$)	(43.33%)
Tuberculosis (02)	6.67%
Toxoplasmosis (11)	36.66%
Non infectious Causes ($n=17$)	(56.67%)
Vogt-Koyanagi-Harada disease (05)	16.67%
Multifocal choroiditis (05)	16.67%
Serpiginous choroidopathy (03)	10.0%
Multiple evanescent white dot syndrome (01)	3.33%
Sarcoidosis (02)	6.67%
Acute posterior multifocal placoid pigment epitheliopathy (01)	3.33%

scans of the macula in various etiological conditions of posterior uveitis are described in Figure 1.

Pre- and posttreatment improvement of visual acuity and CFT in varied etiology of posterior uveitis are presented in Table 3. Our results show that toxoplasmosis choroiditis and VKH cases showed effective outcomes posttreatment.

DISCUSSION

Advances in OCT for retinal imaging help in the quantitative and qualitative assessment of uveitis-related pathology.[8]

Various studies have described the causes of posterior uveitis.[9-13] A comparison of common causes of posterior uveitis with other studies[9-11] is shown in Table 4. Of these studies, Singhs *et al*.[9] found that the most common etiology was serpiginous choroiditis (25.1%), followed by multifocal choroiditis (20.7%) in North India. However, our results are comparable with those of Das *et al*.[10] who found toxoplasmosis as the second most common etiology in 30.3% of cases. In North Africa, Khairallah *et al*.[11] also found toxoplasmosis as the most common cause in 38.3% of cases. Other studies have also reported similar results.[14-16]

Recent studies have reported posterior uveitis secondary to vaccines and immune-inhibitor drugs.[17,18]

Undiagnosed and untreated uveitis causes severe vision loss and even total blindness. However, the visual prognosis of the disease could also depend on the cause of the disease. In our study, we found significant differences in pre- and posttreatment CFT in patients diagnosed with VKH disease and toxoplasma retinochoroiditis, while cases with tuberculosis and sarcoidosis did not show any significant change in CFT.

Table 2: Macular OCT findings in different etiological conditions of posterior uveitis of the included patients

Conditions	OCT findings of our study (Number of cases)
Tuberculosis	Cystoid macular edema (1) Choroidal granuloma (2) Exudative retinal detachment (1)
Toxoplasmosis	Inflammatory precipitates in the vitreoretinal interface. (8) Marked choroidal thickening with retinal necrosis showing ill-defined borders (10) Macular schisis (1)
Vogt-Koyanagi-Harada disease	Presence of subretinal fluid (5)
Multifocal choroiditis	Choroidal thickening and engorgement of choroidal vessels
Serpiginous choroidopathy	Retinal pigment epithelium and choroidal thinning (3) Loss of ellipsoid portion of inner segments and cones outer segment tip lines (2) Atrophy of chorio capillaries (1)
Multiple evanescent white dot syndrome	Disruption of inner-outer segment junction (1)
Sarcoidosis	Choroidal granulomas seen as round hyperreflective structures within the choroidal stroma (2)
Acute posterior multifocal placoid pigment epitheliopathy	Presence of hyperreflective material in outer layers and retinal pigments epithelium with disruption of outer retinal layer (1)

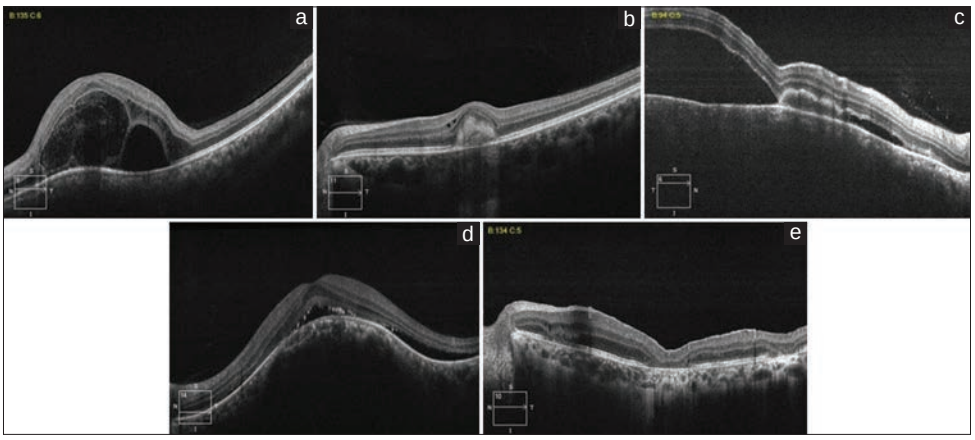


Figure 1: Photographs of macular OCT scans of different etiological conditions of posterior uveitis (a) cystoid macular edema and subretinal fluid in tuberculous choroiditis (b) altered foveal contour with subretinal inflammatory exudates in toxoplasmosis (c) massive subretinal fluid, retinal pigment epithelium, and photoreceptor disruption in Vogt-Koyanagi-Harada disease (d) choroidal granuloma with subretinal inflammatory precipitates in sarcoidosis (e) retinal pigment epithelium and photoreceptor loss in serpiginous choroidopathy

Table 3: Comparison of improvement in pre and posttreatment visual acuity and central foveal thickness in varied etiology of posterior uveitis

Etiology of posterior uveitis (Number of patients)	Pre-treatment		Posttreatment		Mean difference		*P*	
	Visual acuity (Log Mar)	Central foveal thickness (μm)	Visual acuity (Log Mar)	Central foveal thickness (μm)	Visual acuity (Log Mar)	Central foveal thickness (μm)	Visual acuity (Log Mar)	Central foveal thickness (μm)
Toxoplasma retinochoroiditis (11)	1.23±0.47	339.54±90.48	0.93±0.65	222.00±44.70	0.29±0.53	117.5±101.25	**0.099**	**0.003**
MFC (5)	1.00±0.40	365.20±135.57	0.50±0.12	233.40±27.89	0.50±0.41	131.80±131.80	0.054	0.088
Sarcoidosis (2)	1.15±0.92	544.00±404.46	0.89±0.83	320.00±97.58	0.26±0.08	224.00±306.88	0.144	0.490
Serpiginous choroiditis (3)	0.86±0.50	415.33±137.17	0.53±0.30	230.67±31.47	0.33±0.23	184.67±137.17	0.130	0.145
VKH (5)	1.34±0.47	696.20±356.41	0.56±0.56	278.00±99.48	0.78±0.57	418.20±26.14	**0.038**	**0.025**
Tuberculosis (2)	1.54±0.08	341.50±153.44	1.64±0.23	223.50±61.52	-0.10±0.14	118.0±91.92	0.500	0.321
MEWDS (1)	1.00	218.00	0.50	181.00	-	-	-	-
APMPPE (1)	0.80	560.00	0.30	337.00	-	-	-	-

Bold values in the table signify that there was marked improvement in the visual acuity and reduction in central foveal thickness in cases with toxoplasma retinochoroiditis and VKH, MFC: Multifocal choroiditis, VKH: Vogt-Koyanagi-Harada syndrome, MEWDS: Multiple evanescent white dot syndrome, APMPPE: Acute posterior multifocal placoid pigment epitheliopathy

Table 4: Comparison of common causes of posterior uveitis with others studies

Etiology	Our study (%)	Singh *et al*.[9] (%)	Das *et al*.[10] (%)	Khairallah *et al*.[11] (%)
Vogt-Koyanagi-Harada	16.67	-	3.9	4.5
Multifocal choroiditis	16.67	20.7	43.9	-
Toxoplasmosis retinochoroiditis	36.66	8.1	30.3	38.3
Serpiginous Choroiditis	10	25.1	-	5.3
Multiple evanescent white dot syndrome	3.33	-	-	1.5
Sarcoidosis	6.67	-	2.2	-
Tuberculosis	6.67	8.9	0.2	-
Acute posterior multifocal placoid pigment epitheliopathy	3.33	1.6	-	3.8

Patients with toxoplasma retinochoroiditis, VKH disease, and multifocal choroiditis showed visual improvement after treatment. There was no vision improvement in cases with serpiginous choroiditis, tuberculosis, and sarcoidosis due to macular scarring.

In our study, subretinal detachment was the most common type of macular edema. This finding was also observed by Iannatteti *et al*.[8] and Regatieri *et al*.[19] Previous studies have reported OCT findings of posterior hyaloid face precipitates, superficial retinal precipitates and infiltrates, foveolitis, retinitis, neuro-retinitis, choroidal granulomas, and choroiditis in cases with infectious uveitis.[20] In the non-infectious posterior uveitis cases, the reported OCT findings were macular oedema, enlarged deep retinal foveal avascular zone, epiretinal membrane, retinitis, serous retinal detachment, and optic neuritis.[21-23]

To the best of our knowledge, this is the first study conducted in Western India to demonstrate OCT findings in posterior uveitis.

CONCLUSION

Based on our results, it can be concluded that subjecting patients with posterior uveitis to posterior segment OCT as an ancillary diagnostic aid helped in the recognition of a variety of retinal morphological characteristics, which were specific to various inflammatory entities, and could not be identified solely on the basis of ophthalmoscopic examination. These imaging biomarkers facilitated early diagnosis and initiation of specific treatment. Some OCT findings disappeared completely with the resolution of the disease process, while some features were associated with irreversible retinal damage.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Comparison of choroidal thickness in healthy pregnant and preeclamptic women in a tertiary eye care center in Central India: A cross-sectional study

ABSTRACT

Aim: To compare the Subfoveal Choroidal Thickness (SFCT) measured by Enhanced Depth Imaging (EDI) technique of Spectral Domain Optical Coherence Tomography (SD-OCT) in healthy pregnant and preeclamptic women. **Methods:** Our study was cross-sectional hospital-based study in which healthy pregnant women and women having preeclampsia were selected from Obstetrics and Gynecology department and enrolled in it. The guidelines of the American College of Obstetricians and Gynecologists were used to diagnose the cases of preeclampsia. The study included 100 women (200 eyes) which were grouped into 50 healthy pregnant women (group 1), i.e., *n* = 100 eyes and 50 preeclamptic women (group 2), i.e., *n* = 100 eyes. SFCT was measured using the EDI technique of SD-OCT and data were entered in a Microsoft Excel sheet. Statistical analysis was done using Epi Info. Software version 7.2.1.0 (Atlanta, Georgia, US) and the results of both the groups were compared. **Results:** The mean SFCT in both the eyes of the healthy pregnant group and the preeclamptic group was 318.12 ± 37.12 μm and 209.04 ± 26.73 μm, respectively, with a *P*-value 0.001 showing a statistically significant difference between both the groups. **Conclusion:** The SFCT is significantly decreased in preeclamptic pregnant women than in healthy pregnant women.

Keywords: Choroidal thickness, enhanced depth imaging optical coherence tomography, preeclampsia, pregnancy

INTRODUCTION

In normal placentation, embryo-derived cytotrophoblast cells invade the maternal uterine wall leading to remodeling of maternal vessels into high capacitance and low resistance vessels. Also, during normal pregnancy, vascular homeostasis is maintained by physiological levels of vascular endothelial growth factor (VEGF) and transforming growth factor beta-1 (TGF-β1).[1]

In preeclampsia (PE), the invasion of the cytotrophoblasts is incomplete, resulting in constricted, and high resistance vessel formation which cause excess placental secretion of soluble endogenous circulating antiangiogenic proteins inhibiting VEGF and TGF-β1 signaling in the vasculature. These factors cause endothelial cell dysfunction, increasing total peripheral resistance and causing hypertension.[1]

They also affect the endothelial cells of the choroid causing choroidal thinning, fibrinoid necrosis of choriocapillaris, and necrosis of overlying retinal pigment epithelium (RPE), thus causing serous retinal detachment.[1,2]

PE is a serious multisystem-pregnancy-specific syndrome characterized by hypertension, peripheral edema, and proteinuria and is the main cause of maternal and neonatal morbidity and mortality. It can also cause ocular changes,

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including decreased vision, photopsiae, visual field defects, and ocular abnormalities of the conjunctiva, retina, optic nerve, and choroid. Studies have stated that 30–100% of PE pregnancies have retinal and choroidal vascular abnormalities.[3,4] Therefore, choroid evaluation is of vital importance in the management of PE. The incidence of exudative retinal detachment is 1% in PE and 10% in eclampsia.[5] Choroidal thickness (CT) could be an indicator of the severity of PE. To test choroidal function during pregnancy, conventional techniques such as indocyanine green angiography (ICG), fundus fluorescein angiography, and color Doppler ultrasonography were previously utilized.[6] ICG mainly reflects the circulatory state of the choroid and is not suitable for pregnant women due to its invasive nature. With spectral domain optical coherence tomography (SD-OCT), it is difficult to obtain deeper choroidal images due to the limitation of the light source wavelength (800 nm) and the scattering of the light sensor cell layer and RPE. Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) is a newly developed instrument for measuring CT. Being a noninvasive, objective, quantitative, highly sensitive, reliable, and safe diagnostic method, the EDI technique of SD-OCT system has allowed accurate and adequate analysis of choroidal morphological features during pregnancy.[3]

Many similar studies were conducted outside India and in few parts of India but none in central India. Hence, this study was undertaken to compare the SFCT in healthy pregnant and preeclamptic women in central India.

MATERIALS AND METHODS

The study was a cross sectional hospital-based study done in a tertiary eye care center in central India. This study adhered to the tenets of the Declaration of Helsinki, and it was approved by the Institutional Ethical Committee. With reference to the study done by Benfica *et al*.,[7] the sample size was estimated using the formula, $n = (Z_{\alpha/2} + Z_{\beta})^2 * 2^*\sigma^2/d^2$ with mean difference (d): 28.6, power (1-beta) %: 80% and confidence level: 95%.

The final sample size was 100 women (200 eyes) which were grouped into 50 healthy pregnant women (group 1) i.e., $n = 100$ eyes and 50 preeclamptic women (group 2), i.e., $n = 100$ eyes. Healthy pregnant women and diagnosed cases of PE were included from the Obstetrics and Gynecology department. The guidelines of the American College of Obstetricians and Gynecologists were used to diagnose the cases of PE. PE was defined as systolic blood pressure (SBP) of 140 mm Hg or more or diastolic blood pressure (DBP) of 90 mm Hg or more on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal blood pressure and proteinuria with a dipstick reading of 2+ (used only if other quantitative methods not available).[8] Gestation period, gravidity status, blood pressure (BP), proteinuria (by dipstick method), and platelet count data of study subjects were obtained from the Obstetrics and Gynecology ward and accordingly women were enrolled in our study. Women with gestational hypertension in the absence of proteinuria were diagnosed with PE if they presented with any of the following severe features like thrombocytopenia, renal insufficiency, impaired liver enzymes or new onset headache and blurring of vision.[8] Inclusion criteria were healthy pregnant and preeclamptic women from the third trimester with a singleton pregnancy. Exclusion criteria were eclamptic women, patients with a history of ocular trauma, patients who underwent previous ocular surgery, known cases of hypertension and diabetes, patients with Urinary Tract Infection(UTI), autoimmune disorders and other systemic diseases, those with media opacities, macular pathologies like central serous retinopathy, refractive errors with the spherical equivalent greater than ± 1.0 diopters, best-corrected visual acuity of less than 20/20, and intraocular pressure higher than 21 mmHg. Written informed consent was obtained from all the study subjects. The study duration was from September 2020 to September 2022.

All study subjects were brought by the accompanying Obstetrics and Gynecology and Eye department residents in the eye outpatient department on wheelchairs for complete ophthalmic evaluation. A detailed history was taken, and anterior segment examination by Slitlamp bio-microscopy and visual acuity measurement on Snellen's chart was done. Intraocular pressure was measured using a Goldmann applanation tonometer. Fundus and SD-OCT examination by EDI technique was done 30 minutes after the instillation of 1% tropicamide eye drop. All examinations were performed by an experienced ophthalmologist. SFCT (μm) was measured between 10 am and 12 noon to avoid diurnal fluctuations. SFCT was measured using the EDI technique of SD-OCT (Optovue RT Vue-100, 3D OCT System 6.2 version), as the perpendicular distance between the hyperreflective outer border of the RPE and the sclera–choroid interface by a single experienced vitreoretinal surgeon to avoid subjective bias who was also blinded to group identity. Only one single horizontal scan through fovea was used for analysis.

Figure 1 OCT image showing the SFCT in a healthy pregnant woman.

Figure 2 OCT image showing the SFCT in a preeclamptic woman.

Statistical analysis: Data entry was done in a Microsoft Excel sheet and statistical analysis was done using Epi Info. (Software version 7.2.1.0 Atlanta, Georgia, US). The Kruskal–Wallis test was applied for continuous variables and Chi-square test was

applied for aggregative variables. SFCT measurements were presented as mean ± Standard Deviation (SD) (μm). Pearson's correlation coefficient (Rho) was used to determine the correlation between BP and SFCT. Probability (*p*)-value <0.05 was considered statistically significant.

RESULTS

Table 1 summarizes various parameters and clinical features of both the groups like age, gestation period, gravidity status, complaint profile, etc.

Blood pressure: The mean SBP in group 1 women was 122.72 ± 5.65 mmHg and the mean DBP was 78.12 ± 4.65 mmHg. The mean SBP in group 2 women was 154.42 ± 7.37 mmHg and the mean DBP was 99.72 ± 10.7 mmHg. The difference in the mean systolic and DBP between the two groups was statistically significant (*P*-value = 0.001).

Proteinuria: All women in group 1 had trace proteinuria, whereas in group 2, 31 (62%) women had trace proteinuria and 19 (38%) had 2 + proteinuria. The difference in the values of proteinuria between the two groups was statistically significant (*P*-value was 0.001).

Platelet count: The mean platelet count in group 1 women was 233872 ± 95007 count/μL and that in group 2 women was 73160 ± 13692 count/μL. The difference in the mean platelet count between the two groups was statistically significant (*P*-value = 0.001).

Visual acuity, intraocular pressure, and fundus findings: Visual acuity, intraocular pressure, and fundus findings in both the groups were comparable and the difference between the two groups was not statistically significant [Table 1].

Sub-foveal CT: In group 1, the mean SFCT in the right eye was 319.67 ± 37.13 μm and that in the left eye was 316.58 ± 37.56 μm. In group 2, the mean SFCT in the right eye was 208.6 ± 26.5 μm and that in the left eye was 209.46 ± 27.07 μm. In group 1, the mean SFCT in both eyes was 318.12 ± 37.12 μm and in group 2 was 209.04 ± 26.73 μm. The mean SFCT was significantly lesser in preeclamptic pregnant women as compared to healthy pregnant women. The difference in the mean SFCT between the two groups was statistically significant (*P*-value = 0.001).

Figure 3 Bar diagram shows the comparison of mean SFCT in right eye, left eye and both eyes between the two groups.

Correlation between BP and SFCT

Table 2 shows the correlation between the mean SFCT and BP in both the groups.

Table 1: Various parameters and clinical features of both the groups

Characteristics	Mean values		*P*
	Group 1 (50 women) 100 eyes	Group 2 (50 women) 100 eyes	
Age (average±SD) (in years)	25.84±3.94 (Range: 20–38)	27.86±4.86 (Range: 20–42)	
Gestation Period (average±SD)(in weeks)	32.67±2.5 (Range: 29–39)	34.86±3.34 (Range: 28–40)	
Gravidity status			
Primigravida	28 (56%)	40 (80%)	
Multigravida	22 (44%)	10 (20%)	
Complaint profile			
None	50 (100%)	29 (58%)	
Headache, blurring of vision	0	21 (42%)	
Systolic blood pressure (SBP) (mmHg)/Diastolic Blood Pressure (DBP) (mmHg)	122.72±5.65/78.12±4.65	154.42±7.37/99.72±10.7	*P** 0.001
Proteinuria (Dipstick method)			*P*†0.001
Trace	50 (100%)	31 (62%)	
2+	0	19 (38%)	
Platelet count (counts/μl)	233872±95007	73160±13692	*P**0.001
Visual acuity (on Log MAR scale)			*P**0.44
0	8 (16%)	5 (10%)	
0.17	36 (72%)	38 (76%)	
0.3	6 (12%)	7 (14%)	
Intraocular pressure (mmHg)	12.12±2.12	11.48±1.93	*P**0.1
Fundus findings: Normal	50 (100%)	50 (100%)	
Subfoveal choroidal thickness (μm)			*P**0.001
Both eyes	318.12±37.12	209.04±26.73	

SD = standard deviation; * = Kruskal Wallis *p*-value; † = Chi square *p*-value

Table 2: Correlation between the mean SFCT and BP in both the groups

Correlation: Subfoveal choroidal thickness (in μm) Blood pressure (in mm hg)	Groups	Pearson's correlation coefficient (rho)	95% confidence interval	*P*
Subfoveal choroidal thickness Systolic blood pressure	Healthy pregnant	0.15	−0.13–0.41	0.29
	Preeclamptic	0.03	−0.25–0.31	0.827
Subfoveal choroidal thickness Diastolic blood pressure	Healthy pregnant	−0.24	−0.48–0.04	0.098
	Preeclamptic	−0.04	−0.31–0.24	0.80

In both the groups, the mean SFCT (in μm) showed a very weak positive correlation with SBP and a very weak negative correlation with DBP. Thus, the association between SFCT and SBP as well as SFCT and DBP with *P*-value >0.05 was not statistically significant in both the groups.

DISCUSSION

A structurally and functionally normal choroid is critical to retinal functions. Oxygen and glucose are provided to the RPE and outer layers of the retina by choroidal circulation. The choroid also protects the thermal stability of the ocular tissues and removes ocular wastes. The structure and thickness of the choroid can be affected by several factors, different ocular pathologies, and systemic diseases.[4]

The mean age of women in group 1 was 25.84 ± 3.94 years (range: 20–38 years) and that in group 2 was 27.86 ± 4.86 years (range: 20–42 years). In a study conducted by Duru N, *et al*.,[4] the mean age of healthy pregnant women (control group) was 27.54 ± 5.25 years (range: 18–38 years) and the mean age of preeclamptic women (study group) was 29.59 ± 5.43 years (range: 18–43 years).

The mean gestation period in group 1 women was 32.67 ± 2.5 weeks (range: 29–39 weeks) and that in group 2 women was 34.86 ± 3.34 weeks (range: 28–40 weeks). In a study conducted by Duru N, *et al*.,[4] the mean gestation period of healthy pregnant women was 31.98 ± 3.82 weeks (range: 28–39 weeks) and that in preeclamptic pregnant women was 31.81 ± 2.89 weeks (range: 28–37 weeks).

In our study, in group 1, 28 (56%) women were primigravida and 22 (44%) were multigravida and in group 2, 40 (80%) women were primigravida and 10 (20%) were multigravida. Thus, primigravida status was found to be associated with the development of preeclampsia. This finding is consistent with other studies conducted by Teklehaimanot Gereziher Haile *et al*. and Rolv Skjærven *et al*.[4,9,10]

All women in group 1 had no ocular or associated complaints. In group 2, 29 (58%) women had no complaints, but 21 (42%) complained of headaches and blurring of vision. In PE, the central nervous system is most affected due to poor

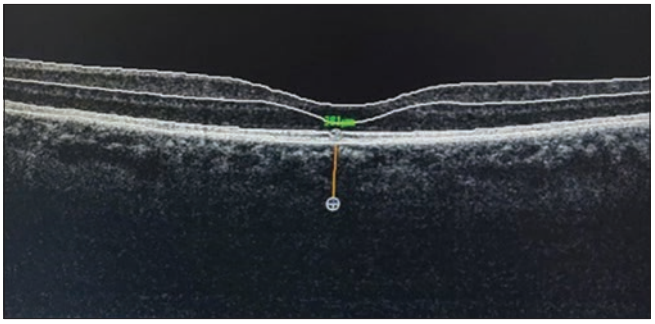


Figure 1: OCT image showing the SFCT in a healthy pregnant woman

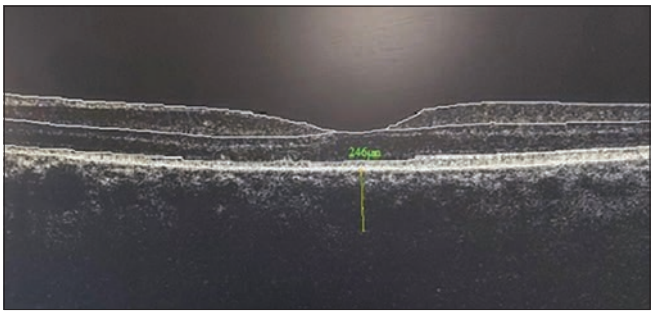


Figure 2: OCT image showing the SFCT in a preeclamptic woman

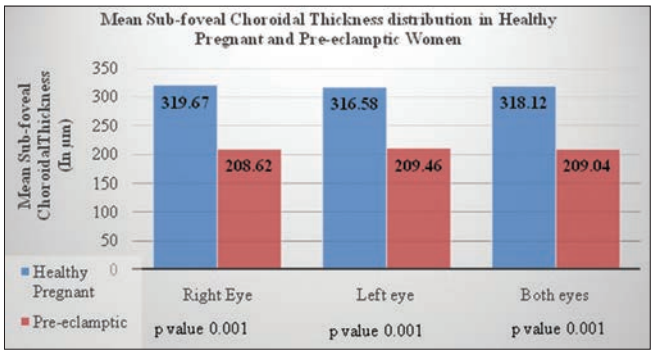


Figure 3: The bar diagram shows the comparison of mean SFCT in right eye, left eye, and both eyes between the two groups

innervation of posterior circulation further disrupting the blood–brain barrier due to acute hypertension and causing vasogenic edema. Patients may present with headaches, convulsions, visual disturbances, and cerebrovascular accidents. Among the visual manifestations, blurring of vision and photopsiae are very common in PE.[11]

The mean SBP in group 1 women was 122.72 ± 5.65 mmHg, and the mean DBP was 78.12 ± 4.65 mmHg. The mean

SBP in group 2 was 154.42 ± 7.37 mmHg, and the mean DBP was 99.72 ± 10.7 mmHg. The difference in the mean SBP and DBP between the two groups was statistically significant (*P* value = 0.001). In a study conducted by Marey *et al*.,[12] the mean SBP in normal pregnant women (group 1) was 118.2 ± 7.33 mmHg and the mean DBP was 77.27 ± 8.83 mmHg, whereas the mean SBP in preeclamptic (group 2) was 147.3 ± 8.83 mmHg and the mean DBP 101.8 ± 7.33 mmHg with *P*-value = 0.001 showing statistically significant difference between the two groups. The results were comparable to the previous study.

All women in group 1 had trace proteinuria, whereas in group 2, 31 (62%) women had trace proteinuria and 19 (38%) had +2 proteinuria. The difference in the values of proteinuria between the two groups was statistically significant (*P*-value = 0.001). A dipstick reading of 2+ was used for the diagnosis of PE when other quantitative method like protein–creatinine ratio was not available. No preeclamptic women had 1+ proteinuria in our study. This variable finding may be because of different maternal hydration statuses.[13]

The mean platelet count in group 1 women was 233872 ± 95007 count/μL and that in group 2 was 73160 ± 13692 count/μL. The difference in the mean platelet count between the two groups was statistically significant (*P*-value = 0.001). Thrombocytopenia associated with hypertensive disorders like PE and eclampsia is the second leading cause of thrombocytopenia in pregnancy.[14]

Choroid being a highly vascular structure, the EDI technique of the SD-OCT system has allowed accurate and adequate analysis of choroidal morphological features during pregnancy.[3] As shown in the results, SFCT of group 1 women was significantly higher than that in group 2. SFCT increase may be related to hormone changes during pregnancy. Kara *et al*.[15] reported that increased blood flow, enhanced arterial compliance, and reduced total vascular resistance during pregnancy may lead to an increase in thickness. Since the choroid is primarily a vascular compartment, changes in hemodynamics during pregnancy may result in fluid retention in the choroid layer associated with pregnancy, thus leading to changes in the CT.[16]

PE is a multisystem disorder causing endothelial damage, increased systemic vascular resistance, and systemic vasospasm, thus changing the CT.[1] Our study found that the mean SFCT of both the eyes in group 1 was 318.12 ± 37.12 μm and that in group 2 was 209.04 ± 26.73 μm. The difference of the mean SFCT between the two groups was statistically significant (*P*-value = 0.001).

Many previous studies measured SFCT in preeclamptic and healthy pregnant women, but the results were controversial. Three studies found that the CT of the preeclampsia group was significantly lower than the normal pregnancy.[3,4,17,18] There are two possible factors that can cause changes in CT in patients with PE. First, preeclampsia is often accompanied by an increase in the systemic vasospasm including the choroid vasospasm leading to the narrowing of the choroidal vascular structure and a reduced blood supply, which may lead to the thinning of the choroid. Second, in patients with PE, the blood pressure increases and the resistance of blood vessels in the whole body, including choroidal blood vessels, increases, which may reduce the blood flow into the choroid resulting in a thinner choroid than that in healthy pregnant women.[3]

In contrast, Kim's study found that the CT of the preeclamptic women was significantly higher than that of the healthy pregnant women. This situation may be because the number of patients Kim *et al*. included was smaller than in other studies (7 preeclamptic women and 14 healthy pregnant women). Another possible reason could be that Kim's study screened only those patients with severe preeclampsia who required Caesarean sections before the planned birth date.[3,19] Also, one study conducted in India, by Lalwani A *et al*.,[6] found that the mean SFCT in preeclamptic women was significantly higher than that in healthy pregnant women. The severe vasoconstriction may have resulted in more significant interstitial edema and increased choroidal vascular hyperpermeability causing an increase in CT.[6,19] Because of the inconvenience and disability of pregnant women, invasive tests such as angiography were not done in these studies. The difference may be because of the limited number of samples and nonuniform severity of PE.[3]

Based on the number of currently available studies, the CT in preeclamptic women was significantly lower than that of healthy pregnant women and results of our study were comparable to the previous studies.

Table 3 shows the comparison of SFCT of our study with previous studies.

In both the groups, the mean SFCT (in μm) showed a very weak positive correlation with SBP and a very weak negative correlation with DBP. Thus, the association between SFCT and SBP as well as SFCT and DBP with *P*-value >0.05 was not statistically significant in both the groups. This finding was contradictory to the study conducted by Marey *et al*.,[12] which showed a significant positive correlation between CT and systemic blood pressure.

Table 3: Comparison of SFCT of our study with previous studies

Studies	Subjects	Gestational age	Mean subfoveal CT (μm)	Conclusions
Duru *et al*.[4]	41 healthy pregnant women 32 preeclamptic pregnant women	31.98±3.82 weeks 31.81±2.89 weeks	389.73±49.64 351.97±22.44 *P*<0.001**	Subfoveal CT in preeclamptic women was significantly thinner than in healthy pregnant women
Lalwani *et al*.[6]	100 Healthy pregnant women 100 Preeclamptic women	33.86±3.14 weeks 34.01±2.92 weeks	294.59±18.03 378.23±20.48 *P*<0.01**	Sub-foveal CT in preeclamptic women was significantly thicker than in healthy pregnant women
Marey *et al*.[12]	11 Healthy pregnant women 11 preeclamptic women	All from third trimester	326.3±30.17 258.9±20.51 *P*=0.018**	Subfoveal CT in preeclamptic women was significantly thinner than in healthy pregnant women
Kim *et al*.[19]	14 Healthy pregnant women 07 preeclamptic women	32.14±2.69 weeks 34.57±16.81 weeks	274.23±29.30 389.79±25.13 *P*=0.000**	Subfoveal CT in preeclamptic women was significantly thicker than in healthy pregnant women
Our study	50 Healthy pregnant women 50 preeclamptic women	32.67±2.5 weeks 34.86±3.34 weeks	318.12±37.12 209.04±26.73 *P*=0.001**	Subfoveal CT in preeclamptic women was significantly thinner than in healthy pregnant women

***P*: Statistically significant

As such, to the best of our knowledge, the present study is the first to assess the SFCT in healthy and preeclamptic pregnant women in central India.

Limitations

Our study has some limitations such as small sample size. In addition, the cross-sectional design of our study allowed us to study SFCT only in the last trimester of pregnancy. Also, the pregnancy period of the included study subjects was more than 28 weeks. At different pregnancy periods, changes in the CT have been found.[20,21] Hence, future prospective longitudinal studies of CT during the three trimesters with more number patients are required to establish the chorio-retinal effects of PE.

CONCLUSIONS

This study has shown that the SFCT measured in preeclamptic women was significantly lower than that of healthy pregnant women. PE being a multisystem pregnancy specific syndrome also affects the ocular structures like the choroid and retina. Hence, we recommend that fundus examination and EDI technique of SD-OCT should be used as a routine screening method in preeclamptic women to evaluate the status of the choroid and retina.

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Key messages

Preeclampsia (PE) is a multisystem pregnancy-specific syndrome, which can affect choroid and retina; Evaluation of choroidal thicknessis is of vital importance in the management of high risk condition of preeclampsia. We recommend EDI technique of SD-OCT imaging, as a non-invasive, highly accurate, safe and reproducible method, in patients of preeclampsia as a routine screening method to measure the choroidal thickness in vivo and understand the morphology of choroid in this pregnancy related condition.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Patterns of ocular morbidity among patients attending leprosy clinic, Siliguri, West Bengal

ABSTRACT

Purpose: To estimate the prevalence and pattern of ocular morbidity among patients attending the leprosy clinic in Siliguri, West Bengal, and identify the risk factors associated with it, if any. **Methods:** It was a clinic-based observational study with a cross-sectional design conducted at Leprosy Clinic, Siliguri, West Bengal among leprosy patients for 1 year from August 2022 to July 2023. Leprosy patients who had completed multi-drug therapy and consented to the study were enrolled. Convenience sampling was performed and the sample size was 117. After a detailed ophthalmic evaluation, the socio-demographic profile of participants and their ocular morbidities were documented and analyzed. A Chi-square test was performed to identify the factors associated with leprosy complications. *P* value < 0.05 was considered statistically significant. **Results:** Overall ocular morbidity for any eye observed was 58.1%. Major findings were cataract (35.9%), aphakia (11.1%), diminished corneal sensation (7.7%), lagophthalmos (7.7%), mild corneal opacity (5.2%), chronic iritis (3.4%), and impaired lid closure (2.6%). Ectropion was present in 2.6% bilaterally. According to the World Health Organization (WHO) criteria for blindness, 11.1% of patients were blind in both eyes. Ocular complications were significantly associated with the respondent's age, duration of disease, classification of disease, and decreased vision. **Conclusions:** The present study shows a significant rate of ocular complications and blindness among leprosy patients. Lid abnormalities, corneal abnormalities, and cataracts were the commonly encountered ocular morbidities among treated leprosy patients.

Keywords: Blindness, cataract, lagophthalmos, leprosy, ocular complication

INTRODUCTION

Leprosy, one of the oldest diseases in mankind's history, caused by *Mycobacterium leprae*, results in lesions of the skin, nasal mucosa, peripheral nerves, and anterior segment of the eye, and may give rise to disabilities and blindness if not treated in time.[1] In 600 BC, the first known written of the disease is mentioned.[2] Ocular manifestations in leprosy have traditionally been categorized as those directly related to leprosy and those that are not directly related to the disease.[3] Almost more than half of the total leprosy sufferers live in India.[4] Though leprosy was eliminated in 2005 as a major public health problem, we are experiencing declining leprosy prevalence. However, new leprosy cases are still being reported from various parts of the world by the WHO. In 2020, 127,558 new leprosy cases were reported from 139 countries.[5] In Eastern India, especially Bihar, Odisha, Chhattisgarh, some parts of Jharkhand, and West Bengal are endemic according to data from the National Leprosy Elimination Programme (NLEP).[6]

Leprosy affects the eye in four ways: i) by direct invasion of lepra bacilli, which may lead to keratitis, iridocyclitis, scleritis, episcleritis, ii) secondary to involvement of the facial nerve (lagophthalmos), and ophthalmic division of the trigeminal nerve (corneal anesthesia), iii) as a part of hypersensitivity reaction causing iridocyclitis, scleritis, and episcleritis, and

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iv) secondary to changes in the skin and support tissue of the lids, tear drainage system (madarosis, trichiasis, entropion, and chronic dacryocystitis).[7] The damage to the optic nerve can cause loss of vision in paucibacillary and lepromatous leprosy. Other ocular complications are cataracts and glaucoma.[8]

There is a lack of published literature on the prevalence and pattern of ocular lesions in leprosy patients in the study area. So, as an important public health topic, the present clinic-based study was undertaken.

Purpose

To find the prevalence and pattern of ocular morbidity among patients attending the leprosy clinic in Siliguri, West Bengal, and identify the risk factors associated with it, if any.

METHODS

Study type and design

This was a clinic-based observational type of study with a cross-sectional design.

Study setting

The study was conducted at the Leprosy Clinic located at Siliguri, which covers leprosy patients from its nearby catchment area, mostly the Siliguri sub-division and nearby districts such as Jalpaiguri, Kalimpong and adjoining areas of Bihar and Nepal. Siliguri is known as the "Gateway of Northeast India," and it is popular for three Ts: tea, timber, and tourism. It is located on the banks of the Mahananda River and the Teesta River at the foothills of the Himalayas.

Study period

This study was conducted for 1 year from August 2022 to July 2023.

Study population

All the diagnosed leprosy patients who had attended the leprosy clinic.

Inclusion criteria

Diagnosed leprosy patients who had completed multi-drug therapy for leprosy and gave consent for the study were enrolled.

Sample size and sampling

Convenience sampling was performed to select patients and the sample size was 117.

Data collection

Before data collection, ethics clearance and permission were obtained from the Institutional Ethics Committee, (Memo no: IEC/NBMC/M-02/10/2022, dated: 01/08/2022), North Bengal Medical College and Hospital, West Bengal, and the Director of Leprosy Clinic respectively. All leprosy patients attending the leprosy clinic were clinically examined by ophthalmic surgeons, optometrists, and ophthalmic assistants. An ocular examination was performed with the help of a slit lamp. A dilated fundus examination was performed in all cases with an indirect ophthalmoscope. Distant visual acuity was tested using Snellen's acuity chart and best-corrected visual acuity was assessed by an optometrist. The participants were examined for lid changes such as entropion, ectropion, lagophthalmos, trichiasis, and impaired eyelid closure. Similarly, cornea, conjunctiva, sclera, and lens of the eyes were examined in detail for complications. Patients with complicated ocular lesions were referred to North Bengal Medical College and Hospital, where morbidities such as refractive error were corrected by prescribing glasses, and dry eye-like conditions were treated by prescribing tear substitutes. Lagophthalmos and complicated cataracts were treated by tarsorrhaphy and cataract extraction followed by intraocular lens implantation.

Ocular complications related to leprosy included diminished corneal sensation, corneal opacity, ectropion, entropion, trichiasis, lagophthalmos, acute/chronic iritis, iris atrophy, and synechiae. Pterygium, cataracts, aphakia, and pseudophakia were included in the general ocular complications. Lagophthalmos or severe corneal or iris disease was defined as sight-threatening ocular complications.[9] The WHO classified the decreased vision as a corrected Snellens' visual acuity of 6/18 and the blindness used was 3/60. The overall prevalence of ocular morbidities was estimated as whether present in one or both eyes.

Data analysis

Collected data were checked for completeness, coded, and entered into the Microsoft Office Excel (2013) data sheet and then it was exported to the IBM Statistical Package for Social Sciences version 22 for analysis. A Chi-square test was performed to identify the factors associated with leprosy complications. P value < 0.05 was considered statistically significant.

RESULTS

In the present study, 117 patients were studied and the majority (87, 74.4%) patients were male. Patient's ages ranged from 20 to 80 years with a mean age of 52.3 years and a standard deviation of ± 14.02 years. The majority (53, 45.3%) of patients belonged to the age group 41 to 60 years. Regarding the distribution of caste and education level of patients, the most common being from the scheduled

tribe (40, 34.2%) and illiterate (63, 53.8). Occupational data were available for all patients, 40 patients (34.2%) were unskilled workers, followed by 30 patients (25.6%) who were unemployed or students, 26 patients (22.2%) were skilled workers, and 21 (18.0%) looked after the home. A total of 100 patients (85.5%) had multi-bacillary (MB) leprosy disease and 17 patients (14.5%) had pauci-bacilliary (PB) leprosy disease. The duration of the disease ranged from 1 year to 52 years. The mean duration was 18.3 years with a standard deviation of ±15.3 years. This was further subdivided into duration of less than 5 years for 37 patients (31.6%), 5–20 years for 32 patients (27.4%), and more than 20 years for 48 patients (41.0%) [Table 1].

In the present study, the overall prevalence of ocular morbidities for any eye among the leprosy patients found was 58.1% [Figure 1].

On ocular examination, it was observed that 72 patients (61.5%) had visual acuity less than 6/18, or better, in both eyes. Only one patient had vision less than 3/60 in one eye. Blindness (<3/60) in both eyes was noted in 13 patients (11.1%) [Table 2].

Ocular complications, that is, cataract (42 patients, 35.9%), aphakia (13 patients, 11.1%), diminished corneal sensation (9 patients, 7.7%), lagophthalmos (9 patients, 7.7%), mild corneal opacity (6 patients, 5.2%), chronic iritis (4 patients, 3.4%), impaired lid closure (3 patients, 2.6%), ectropion (3 patients, 2.6%), and trichiasis (2 patients, 1.7%) were most commonly observed in the study [Table 3].

Primary ocular complications were tested with a Chi-square test against the potential confounders and risk factors of age, duration of disease, classification of disease, and decreased vision. Leprosy complication was significantly associated with increasing age (χ^2 =17.068, df = 2, P = <0.001) and with an increase in the duration of the disease (χ^2 =9.061, df = 2, P = 0.011). Leprosy complication was observed more in the multi-bacillary leprosy and it was statistically significant (χ^2 =4.257, df = 1, P = 0.039). Decreased vision and vision less than 3/60 were significantly associated with leprosy complications (χ^2 =45.651, df = 2, $P \leq 0.001$) [Table 4].

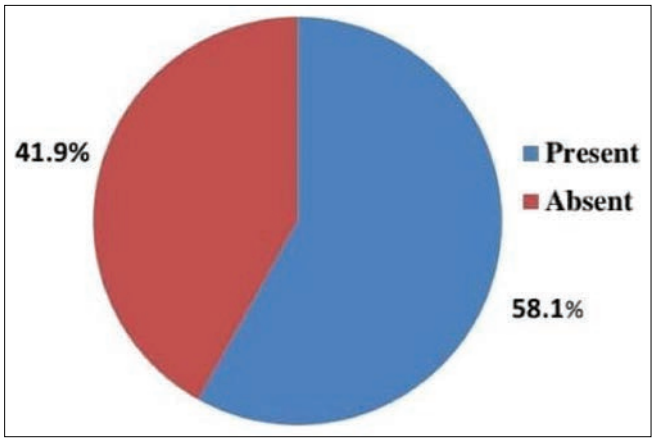


Figure 1: Prevalence of ocular morbidity among leprosy patients (*n*=117)

DISCUSSION

The WHO declared that leprosy was eliminated globally in 2001; however, pockets of high endemicity remain, primarily in a few developing countries.[10]

In the present study, the overall prevalence of ocular morbidity in any one eye was 58.1%, which was similar to the study conducted by Kasugur *et al.,* in which 58% of patients had anyone ocular morbidity.[11] Similar studies conducted by Daniel *et al.*, Courtright *et al.,* and Thompson *et al.* observed that the rate was between 57% and 66% of patients having any type of ocular complication.[12-14] Another

Table 1: Background characteristics of the study participants (*n*=117)

Characteristics	Frequency	Percentage
Age Group (In years)		
20–40	27	23.1
41–60	53	45.3
>60	37	31.6
Sex		
Male	87	74.4
Female	30	25.6
Caste		
General	25	21.4
Scheduled Caste	21	17.9
Scheduled Tribe	40	34.2
OBC	31	26.5
Education level		
Illiterate	63	53.8
Primary school	24	20.5
Middle school	20	17.1
Secondary & above	10	8.5
Occupation		
Unskilled worker	40	34.2
Skilled worker	26	22.2
Homemaker	21	18.0
Unemployed	30	25.6
Types of leprosy		
Pauci - bacillary	17	14.5
Multi - bacillary	100	85.5
Duration of disease (In years)		
<5	37	31.6
5–20	32	27.4
>20	48	41.0
Total	117	100.0

Table 2: Distribution of visual acuity among the study participants (*n*=117)

Visual Acuity (VA group)	Right eye *n* (%)	Left eye *n* (%)
<6/18	73 (62.4)	72 (61.5)
6/18–3/60	30 (25.6)	32 (27.4)
<3/60	14 (12.0)	13 (11.1)
Total	117 (100)	117 (100)

Parenthesis shows column percentage

Table 3: Ocular complications seen in leprosy patients (*n*=117)

Ocular complications*	Frequency	Percentage
Lids		
Ectopion	3	2.6
Entropion	1	0.9
Lagophthalmos	9	7.7
Trichiasis	2	1.7
Lid closure		
Impaired	3	2.6
Absent	0	0.0
Corneal sensation		
Diminished	9	7.7
Absent	3	2.6
Corneal opacity		
Pannus	0	0.0
Mild	6	5.2
Moderate	2	1.7
Severe	1	0.9
Pterygium	2	1.7
Iris		
Atrophy	0	0.0
Acute iritis	0	0.0
Chronic iritis	4	3.4
Lens		
Cataract	42	35.9
Aphakia	13	11.1
Psuedophakia	3	2.6

*Ocular complications were counted as present whether present in eye or both eyes

study conducted by Ffytche[15] also found that 24.3% of the patients had sight-threatening ocular complications even after the completion of MDT.

According to the WHO criteria for blindness, 12% of patients were blind and 27.4% had moderate visual impairment in the present study. Corneal opacity, cataracts, or combinations of both were the main causes of blindness, whereas, similar studies were conducted by Shrestha *et al.* and Thompson *et al.* in which 2.9% of subjects were blind and 20.7% to 27.1% had moderate visual impairment.[14,16] The multicentre study conducted by Thompson *et al.* found a blindness rate of 3.2% and the study by Ffytche reported a blindness prevalence of 2.9%.[14,15] In the present study, the most common leprosy-related ocular complications in 22.2% of patients were diminished corneal sensation (7.7%), lagophthalmos (7.7%), mild corneal opacity (5.2%), chronic iritis (3.4%), impaired lid closure (2.6%), and ectropion (2.6%). Similar findings were observed in the study by Shrestha *et al.* in Nepal.[16] In another largest cross-sectional study among leprosy patients, 23.1% have leprosy-related eye disease including 13.5% having lagophthalmos, 1.2% having uveitis, and 14.1% having diminished corneal sensation.[17] In another study conducted by Ray *et al.*[18] in Burdwan, leprosy-related ocular complication was observed in 64% and lagophthalmos in 20%.

More than one lesion was observed among the participants with ocular involvement. Potentially sight-threatening lesions were lagophthalmos, corneal opacity, and cataracts. However, in the present study, 35.9% of the participants had cataracts and the majority of them were in the age group of 41 to 60 years and above 60 years. Cataracts may be due to age, prolonged use of steroids during the treatment of leprosy, and as a complication of chronic iridocyclitis. Similar findings were observed in the study by Malik and Morris.[19]

In our study, aphakia was found in 11.1% of the study participants and it may be due to previous surgical complications. These aphakic study participants had a history of previous cataract surgery.

In the present study, the prevalence of ocular complications was found higher in multi-bacillary leprosy with an increased duration of disease, which was similar to other studies.[14,20,21] Daniel *et al.*[22] found that 5.6% of multi-bacillary leprosy patients, who had completed MDT, could develop new ocular complications of the disease.

In the present study, sight-threatening ocular complications and blindness were at relatively higher rates; this may be because of the mixed patient population, some patients had been suffering from leprosy for a long duration (range: 0–52 years, mean: 18.3 years) and which was similar to the study by Malik and Morris.[19]

Ocular complications were found statistically significant with the potential risk factors, that is, age, duration of disease, classification of disease, and decreased vision, which were similar to the study conducted by Malik and Morris.[19]

Leprosy is a chronic disease with disabling complications that involve ocular permanent and may progress long even after treatment has been completed. In our study, lid abnormalities, corneal abnormalities, and cataracts were the commonly encountered ocular morbidities among leprosy patients. Patients are at risk of life-long, sight-threatening ocular complications because symptoms can often be delayed

Table 4: Factors associated with the prevalence of ocular morbidity among leprosy patients (n=117)

Variables/Ocular morbidity	Ocular morbidity		Total (%)	Chi square test
	Present (%)	Absent (%)		
Age group (In years)				
20–40	8 (6.9)	19 (16.2)	27 (23.1)	χ^2=17.068
41–60	30 (25.6)	23 (19.7)	53 (45.3)	df=2
>60	30 (25.6)	7 (6.0)	37 (31.6)	$P\leq$0.001*
Duration of disease (In years)				
<5 years	15 (12.8)	22 (18.8)	37 (31.6)	χ^2=9.061
5–20 years	18 (15.4)	14 (12.0)	32 (27.4)	df=2
>20 years	35 (29.9)	13 (11.1)	48 (41.0)	P=0.011*
Types of leprosy				
Pauci-bacillary	6 (5.1)	11 (9.4)	17 (14.5)	χ^2=4.257 df=1
Multi-bacillary	62 (53.0)	38 (32.5)	100 (85.5)	P=0.039*
Visual acuity (VA group)				
<18/60	25 (21.4)	48 (41.0)	73 (62.4)	χ^2=45.651
18/60–3/60	30 (25.6)	00 (00)	30 (25.6)	df=2
<3/60	13 (11.1)	1 (0.9)	14 (12.0)	$P\leq$0.001*

Parenthesis shows row percentage, *statistically significant

due to corneal insensitivity, which masks some ocular symptoms. There is a need for periodic ophthalmological examination and follow-up for all leprosy patients and to generate awareness of new eye symptoms and signs among the patients.

Limitations

The small sample size and lack of investigations for other causes of chronic iritis were our major study limitations.

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Conflicts of interest

There are no conflicts of interest.

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‘From sun to lasers’: The story of retinal photocoagulation

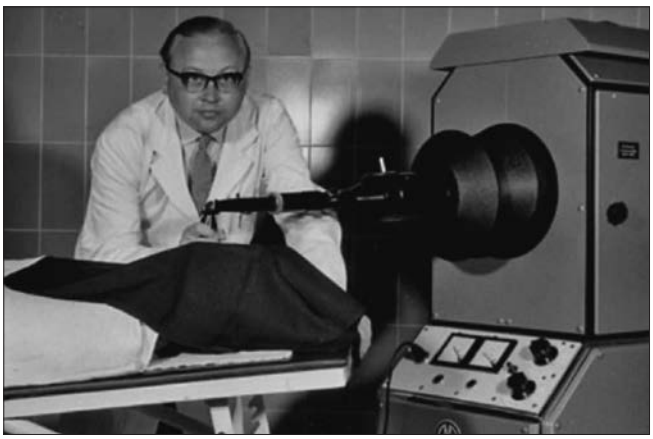


Figure 1: Dr. Meyer-Schwickerath performing retinal photocoagulation using Xenon photocoagulator

This iconic photograph [Figure 1] features Gerhard Meyer-Schwickerath using a xenon photocoagulator to coagulate the retina. Retinal photocoagulation is one of the most common procedures done in ophthalmology and owes the origins to the observations and experiments done by the pioneering ophthalmologist Dr. Gerhard Meyer-Schwickerath.

Born on September 10, 1920, in Elberfeld, Germany, Dr. Meyer-Schwickerath started his career as a medic treating soldiers injured in the frontlines of World War II. Following the war, he worked at the University of Hamburg-Eppendorf’s eye clinic and received his postdoctoral degree and professorship at the University of Bonn in 1953. Later, Dr. Meyer-Schwickerath became the director of the Ophthalmology Center at the Essen University Hospital, where he later served as the director and worked as a professor at the University of Münster until his retirement.[1]

Dr. Meyer-Schwickerath had the opportunity to treat a few patients who had developed retinal damage following the solar eclipse on July 10, 1945.[2] He became intrigued with the retinal scars they developed and began to work on the possibilities of using light to scar the retina and its potential applications in treating retinal detachments. This was a landmark project, which paved the way for beginning of retinal LASERs in ophthalmology.

Dr. Meyer-Schwickerath started his experiments using a self-fashioned heliostat, which was used to reflect sunlight through a Galilean telescope, fixed in his operating room.[2] The heliostat was used to provide optimal sunlight according to the sun’s movement throughout the day. The first successful photocoagulation took place in 1949. The major challenge during his initial experiments was the possibility of obtaining adequate viable tissue to preserve vision due to severe traumatic retinal burns following photocoagulation.

With further research, Dr. Meyer-Schwickerath observed that light of wavelengths 400–900 nm could pass through the cornea and lens of the eye without loss of sufficient energy.[2,3] In the 1950s, high-pressure xenon lamps and photocoagulation were used instead of sunlight.[3]

Meyer-Schwickerath received honorary doctorates from several universities and was nominated thrice for the Nobel Prize. Gerhard Meyer-Schwickerath passed away at the age of 71 on January 20, 1992 in Essen.

From the initial days of retinal photocoagulation, when Dr. Gerhard Meyer-Schwickerath used to take patients to the

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roof of his laboratory in 1949 and used focused sunlight on their retinas to treat melanomas, retinal phototherapy has gone a long way forward. Nonsolar sources like the xenon arc photocoagulator became available by the mid-1950s and were effective for sealing retinal breaks and treating tumors. But it was more traumatic, creating large and severe burns, and hard to use.

The development of LASER in 1960 by Maiman revolutionized precision and control of light delivery in retinal photocoagulation. The first report on making ocular lesions with a ruby LASER was published the next year, but it was less successful practically.

The discovery of the argon LASER by Bridges in 1964 provided blue (488 nm) and green (514 nm) wavelengths and had the advantage of being strongly absorbed by hemoglobin and melanin. Further progress was achieved when the LASER could be coupled to a slit lamp (Little *et al*. 1970). Argon LASER trabeculoplasty (Teichmann *et al*. 1976, Wise and Witter 1979) and iridectomy (Beckman and Sugar 1973) were later.[4]

Continuous advancements in LASER technologies, along with discoveries of various tissue response pathways, have improved the precision and selectivity of LASER therapy. Dr. Meyer-Schwickerath remains the doyen whose astute intellect and observations paved way for further advancements in the field of retinal photocoagulation.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Waardenburg or Blepharophimosis ptosis epicanthus inversus syndrome? – An enigmatic riddle

ABSTRACT

Waardenburg syndrome (WS) is a genetic disorder that may be discernible right at birth. The syndrome is well known to have heterogeneous expression; the range, and severity of which may vary greatly from case to case, even among the individuals of the same household. Here, we report a 19-year-old female who was initially diagnosed as a case of Blepharophimosis ptosis epicanthus inversus syndrome (BPES) and referred to our subspecialty clinic for undergoing surgery. On examination, she had medial canthal dystopia, telecanthus, synorphys, and similar facial features in a first-degree family member. These features were suggestive of WS. After that, the primary diagnosis was revised; systematic evaluation was performed, surgical correction for her telecanthus was ventured with a favourable outcome. Both WS and BPES may present with similar facial features and thereby pose a clinical dilemma. Such misdiagnosis may hinder proper evaluation and management of any underlying systemic associations.

Keywords: Blepharophimosis, BPES, telecanthus, Waardenburg syndrome

INTRODUCTION

Telecanthus or dystopia canthi as proposed by Mustarde, is an increase in the distance between medial canthus with lateral displacement of lacrimal puncta without an increase in interpupillary or inter lateral canthal distance.[1] Telecanthus occurs due to abnormal insertion or lengthening of the medial canthal tendon. Commonly associated congenital disorders with telecanthus include Down syndrome, fetal alcohol syndrome, Cri du Chat syndrome, Klinefelter syndrome, Turner syndrome, Ehlers-Danlos syndrome, and Waardenburg syndrome (WS). Hypertelorism is the true lateralization of the bony orbit, characterized by increased intercanthal distance, outer canthal distance, and interpupillary distance. Hypertelorism is present in a variety of conditions like craniofacial clefts, craniofacial dysplasias, and craniosynostosis syndromes such as Apert and Crouzon's syndrome.[2] WS or Van der Hoeve–Halbertsma–Waardenburg–Klein syndrome is a rare genetic condition characterized by combined features of ocular and associated systemic anomalies.[1] The characteristic features as reported by Petrus Johannes, Waardenburg included telecanthus (90%), hyperplasia supercili medialis (45%), radices nasi (78%), heterochromia iridis (25%), hearing defect (20%), and median white forelock (17%).[1]

CASE PRESENTATION

A 19-year-old female presented to the outpatient department with complaints of a broad nasal bridge since birth [Figure 1a]. She visited a local ophthalmologist, where she was diagnosed with Blepharophimosis ptosis epicanthus inversus syndrome (BPES); and was referred to the oculoplastic clinic of

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our tertiary centre for undergoing surgery. On further enquiry, we found that there were similar features in her father and grandfather as well; however, there was no history of any systemic illness or developmental delay.

On general examination, she was noted to have few white hairs near her forehead but mostly were dyed brown. She had a synorphys with prominent bushy eyebrows, she had narrow nostrils, and her philtrum was small. There were no musculoskeletal, cardiac, and gastrointestinal abnormalities.

On ophthalmological examination, a widened bridge of nose with medial canthal dystopia was noted with pseudoesotropia of the left eye. &*&The Waardenburg index (WI) is a biometric index for diagnosing WS when values are >1.95. (a) Inner canthal, (b) interpupillary, and (c) outer canthal distances were measured using a rigid ruler held against face to calculate Waardenburg index (WI = $X + Y + a/b$) where $X = (2a - 0.2119c - 3.909)/c$ and $Y = (2a - 0.24719b - 3.909)/b$.[3] In our case, $a = 50$ mm, $b = 66$ mm, $c = 100$ mm and thus WI index was 2.31. She had right-sided mild and left-sided moderate congenital ptosis.

On ocular examination, best corrected visual acuity was noted to be 6/6 in both eyes and intraocular pressures were 12 mm Hg and 16 mm Hg in the right and left eye, respectively. The anterior segment of both eyes was within normal limits. There was no evidence of any heterochromia of iris. On fundus examination, there was a mild chorioretinal degeneration and peripapillary atrophy in both eyes. Based on the presence of telecanthus, associated facial features, and a history of similar symptoms in first-degree relatives, a diagnosis of WS was made.

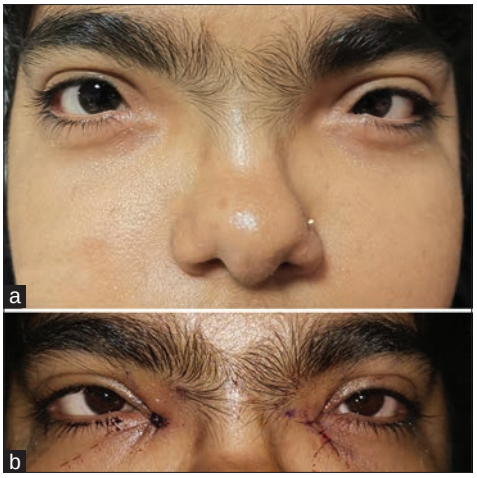


Figure 1: (a) Clinical picture of the patient showing synorphys, bushy eyebrows, medial canthal dystopia, pseudoesotropia, small nostrils, and smooth philtrum. (b) Clinical picture of the patient showing correction of medial canthal dystopia

The patient had a normal intelligence quotient (IQ) and was evaluated for sensorineural hearing loss by using pure tone audiometry which came out to be normal. She eventually underwent medial canthoplasty with medial canthal tendon plication for telecanthus and had a satisfactory outcome [Figure 1b].

DISCUSSION

WS occurs due to abnormality in neural crest cell migration and has an autosomal dominant mode of inheritance with an imperative complete penetrance and variable expression; however, autosomal recessive patterns have also been reported. The prevalence varies from 1:20000 to 1:40000.[4] The diagnostic criteria[5] for WS is given in Table 1.

WS is characterized by the absence of melanocytes affecting hair, eyes, stria vascularis of cochlea, and skin resulting in various features, such as skin hypopigmentation, white forelock, heterochromia iridis, and sensorineural hearing loss. It has been further classified into four types based on genetics and associated systemic anomalies. Type I WS is attributed to a loss of function mutation of the PAX 3 gene. Type II WS is caused by a mutation in microphthalmia associated transcription factor (MITF) gene responsible for melanogenesis. Type III WS (Klein- WS) is an extreme presentation of Type I WS characterized by abnormalities of arms with some patients being homozygotes. Mutation in the genes like endothelin-3 or one of its receptors, EDNRB lead to Type IV WS (Shah WS with Hirschsprung).[6]

Type I WS patient most commonly presents with a wide space between the inner canthus associated with hearing impairment in only 20% of cases.[7] However, the phenotype of WS Type I varies even among family members. Type II WS is characterized by pigmentary abnormalities, congenital non-progressive SNHL, and absence of dystopia canthorum (commonly seen in Type I).[8] Other features

Table 1: Diagnostic criteria of WS

Major Criteria	Minor Criteria
Congenital sensorineural hearing loss	Synophrys and/or medial eyebrow flare
White forelock, hair hypopigmentation	Broad/high nasal root, low hanging columella
Pigmentation abnormality of iris	Underdeveloped alae nasi
Complete heterochromia	
Partial heterochromia	
Hypoplastic blue irides or brilliant blue irides	
Dystopia canthorum	Premature gray hair
Affected first-degree relative	Congenital leukoderma

A clinical diagnosis is made in the presence of two major criteria or one major plus two minor criteria

like white forelock, synorphys, nasal root hypoplasia, and leukoderma are more frequent in WS I.

Type III WS is characterized by bony abnormalities like syndactyly, hypoplasia of the musculoskeletal system, flexion contractures, fusion of carpal bones, and winged scapula. Type IV WS is characterized by pigmentary abnormalities, hearing loss, and Hirschsprung disease.[7] WS 4 can be further subdivided into three categories, subtype 4A, 4B, and 4C having mutations in the endothelin receptor type B gene (chromosome 13), endothelin 3 (chromosome 20), and SOX10 (chromosome 22) genes, respectively. Type I and Type II WS are commonly encountered in daily practice.

Our patient was initially misdiagnosed as a case of BPES. BPES is characterized by horizontal shortening of the palpebral fissure known as blepharophimosis, ptosis with poor levator function, and prominent epicanthus inversus.[8,9] They have telecanthus as well, which must have led to the confusion in diagnosis. However, the ocular condition in WS does not have ptosis or epicanthus inversus. Our case was a Type I WS with features of telecanthus, a family history of similar illness, and a history of the white forelock.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

Right inferior rectus palsy – An unusual initial presentation of a case of disseminated fungal infection

ABSTRACT

Orbital Aspergillosis is a rare life-threatening fungal infection that is often misdiagnosed due to its nonspecific clinical and radiological appearance. In this case report, we present a case of disseminated aspergillus infection initially presenting as right inferior rectus palsy.

Keywords: Aspergillus, extraocular, fungal, infection

INTRODUCTION

There are multiple causes of extraocular muscle palsy out of which fungal infection is an important etiology affecting both immune-compromised and otherwise healthy patients. It mostly presents as unilateral orbital mass, which can cause eyelid swelling, proptosis, extraocular muscle palsy, or optic nerve compression. Delayed diagnosis or inappropriate treatment can cause vision loss or can even be fatal to the patient. The therapeutic options range from conservative antifungal to radical surgical debulking.

The diagnosis of fungal infection is difficult due to multitude of possible etiology, however with recent surge in such cases after covid-19 infections, any T2 hypointense lesion has to be seen with suspicion for fungal infection apart from other granulomatous etiologies, such as tuberculosis. In this case report, we present a case of disseminated aspergillus infection initially presenting with right inferior rectus palsy and later found to have concomitant infection of brain parenchyma, cervical, and mediastinal lymph nodes.

CASE HISTORY

A 36 year old male patient presented with right eye diplopia for 15 days. On examination, inferior gaze palsy was found. There was no associated proptosis. There was short duration history of ocular pain and headache, but no fever. Patient did not have any other significant complaint. Also there was no lymphadenopathy or any other palpable swelling. Patient was nondiabetic. There was no history of immune-compromised status. Blood investigations were unremarkable except mildly elevated erythrocyte sedimentation rate and total leucocyte count.

For further evaluation, patient underwent magnetic resonance imaging (MRI) study for head and orbits. MRI revealed bulky and STIR hyperintense right inferior rectus muscle [Image 1]. Rest of the extraocular muscles were normal. Retrobulbar fat planes were normal. Left orbit was normal. Incidentally detected intracranial findings included irregular conglomerated avidly enhancing nodular and plaque like lesions in right parietal lobe with lesions distributed along cerebral cortex/gray-white

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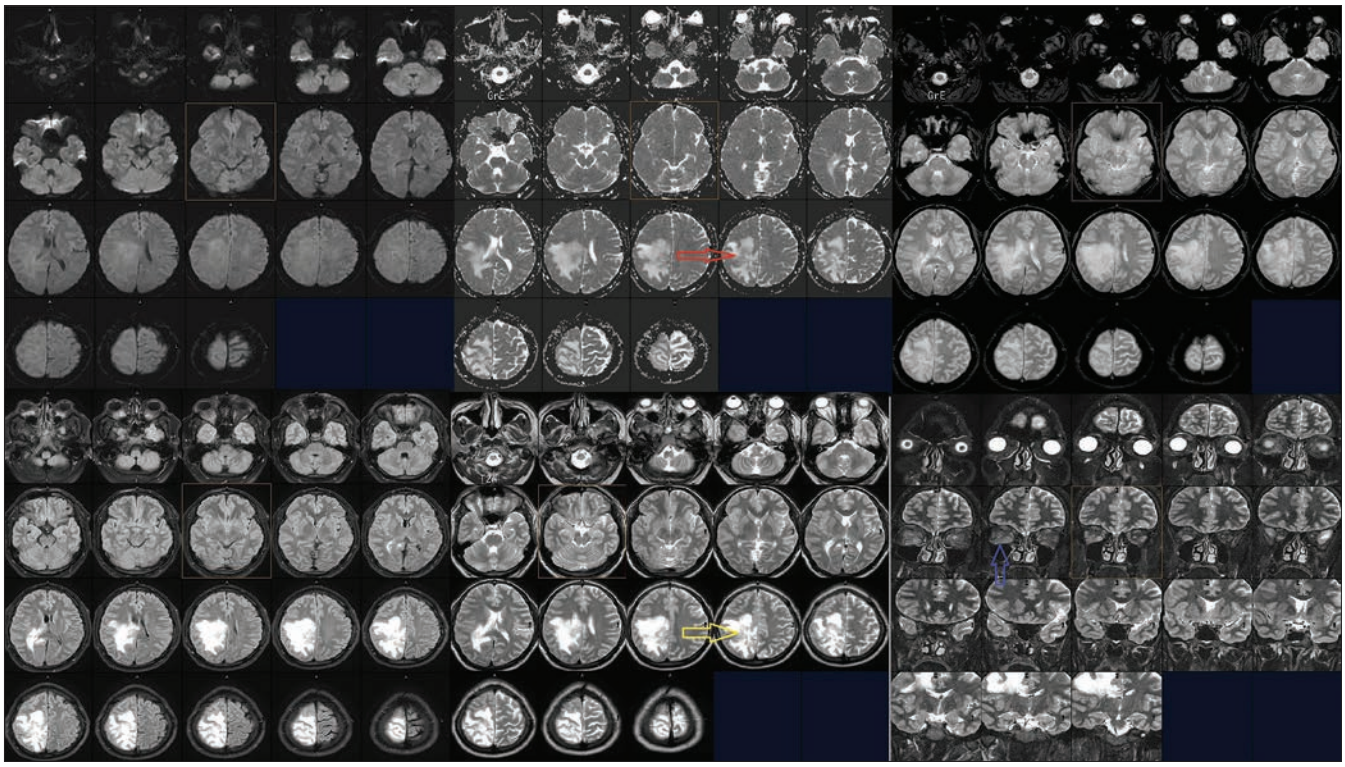


Image 1: Axial DWI, ADC, GRE, FLAIR, T2W images of brain showing T2 hypointense lesion in right parietal lobe with perilesional edema (yellow arrow). STIR coronal image of orbit showing bulky right inferior rectus muscle with hyperintense signal (blue arrow)

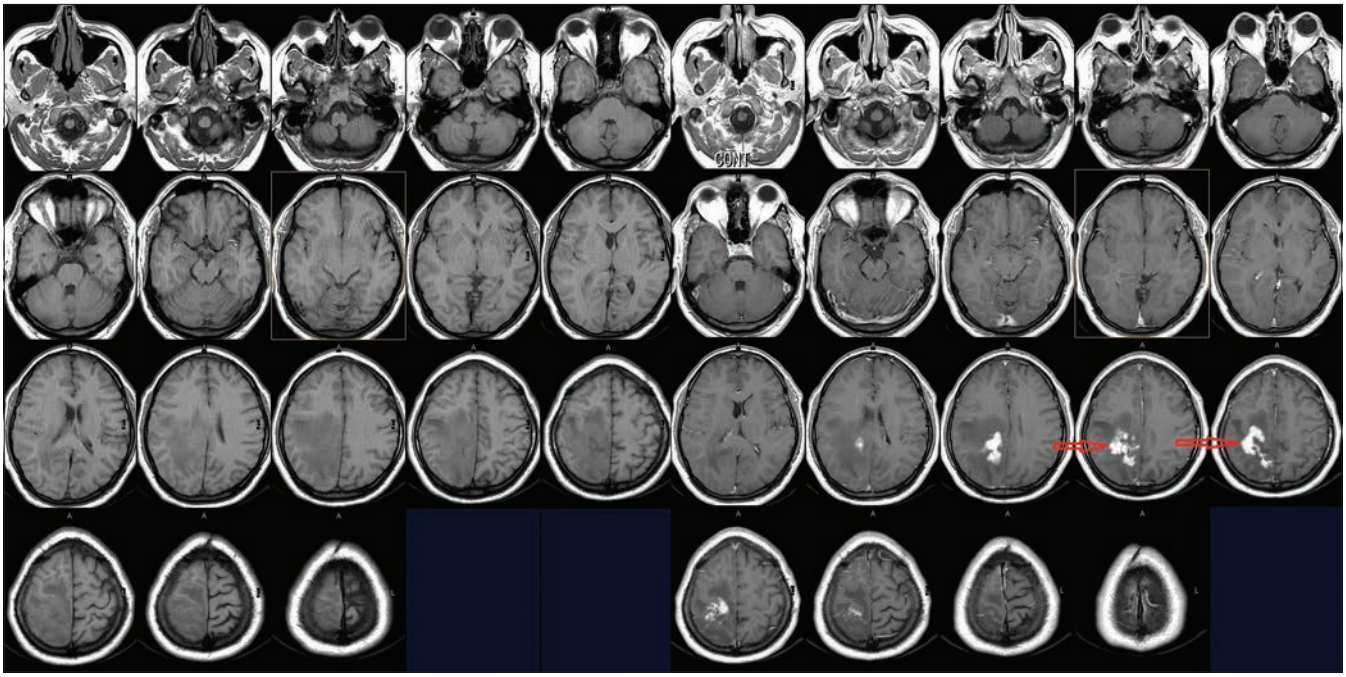


Image 2: Pre- and post-contrast T1W images showing conglomerated irregular nodular and plaque like lesions in right parietal lobe with irregular enhancing margins

matter junction, with effaced regional sulcal spaces [Images 1 and 2]. Regional leptomeningeal hyperenhancement was noted along effaced sulci. On T2-weighted images (WI) and noncontrast T1WI, lesions were of intermediate signal intensity and poorly defined. Lesions were also not showing diffusion restriction. MR spectroscopy [Image 3] revealed lactate peak along elevated choline peak and a nonspecific peak at 1.5 ppm. There was no lipid peak. Associated

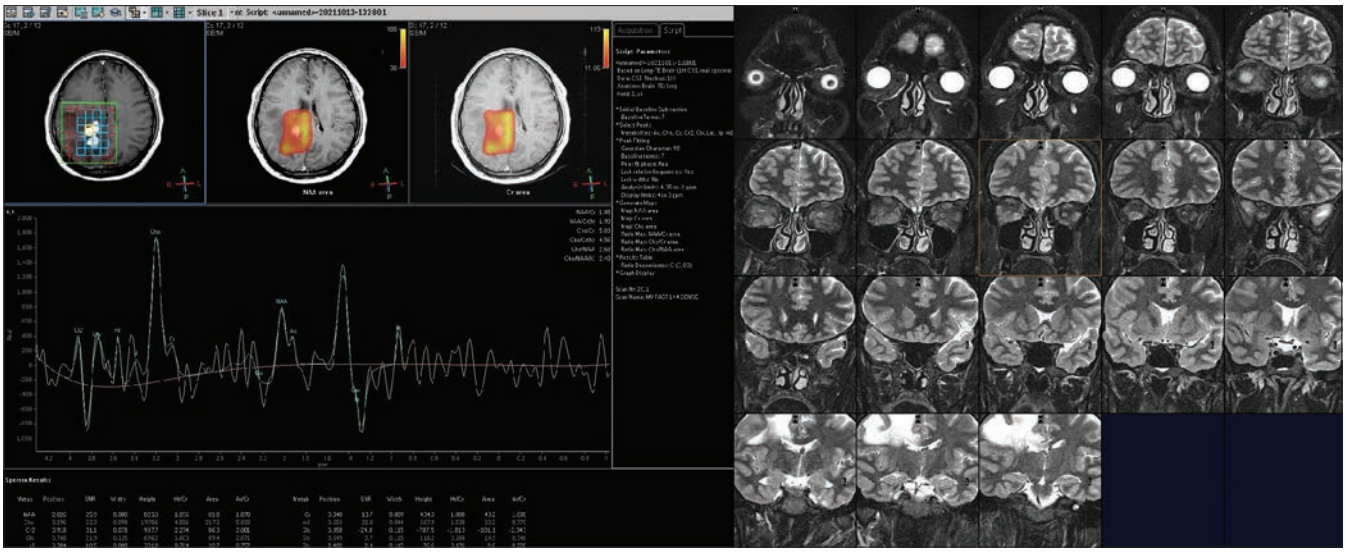


Image 3: MR spectroscopy at intermediate TE (145 ms) showing lactate peak along with elevated choline peak and a nonspecific peak at 1.5 ppm. STIR coronal image of orbit showing bulky and hyperintense right inferior rectus muscle

moderate perilesional white matter edema was noted in the form of T2/FLAIR hyperintensity and there was no diffusion restriction. In view of these findings possibilities of lymphoma and granulomatous diseases including fungal and tubercular etiologies were given.

Patient was referred to a higher center for further management. Fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) was done as next line of imaging investigation to look for extent and disease dissemination. It revealed metabolically active lesions in right parietal lobe of brain, right orbit (inferior rectus), and left level V lymph nodes of neck along with metabolically active mediastinal lymphadenopathy. Mediastinal lymphadenopathy was non-necrotic homogeneously enhancing type with conglomerated nodes and nodal masses [Image 4]. Nodal masses were also involving pericardial recesses along roots of major mediastinal vessels. There was no metabolically active lesion in lungs. Few patchy fibrotic patches were noted in the right lung. There was no pleural or pericardial effusion.

With this, differentials remained same including lymphoma and granulomatous disease. Further Fine needle aspiration cytology (FNAC) was done from left level V cervical lymph nodes which turned out to be inconclusive. Later, in view of raised intracranial tension, patient underwent decompressive craniectomy and also biopsy was done from right parietal lesions. Biopsy from intracranial lesion revealed inflammatory infiltrates with multinucleated giant cells and septate fungal hyphae suggestive of fungal infection (morphology favoring Aspergillus).

So final diagnosis was disseminated fungal infection (Aspergillus) with involvement of brain, orbit (extraocular muscles), cervical lymph nodes, and mediastinum. Unfortunately, patient did not survive despite antifungal treatment. There was no history of recent covid infection.

DISCUSSION

Disseminated invasive fungal infections are not uncommon in immunocompromised patients, however these infections are uncommon (or rare) in immunocompetent individuals. Presentation can be slow and nonspecific leading to delayed diagnosis.

Our patient had right eye diplopia as presenting feature, but thereafter patient's clinical condition worsened rapidly, and despite diagnosis and treatment, patient succumbed to illness. In this case, orbital involvement manifested first, with comprehensive imaging evaluation revealing intracranial involvement along with cervical and mediastinal nodal disease.

Multisite craniofacial and orbital involvement have been reported in many fungal infections.

Rammurti *et al.*[1] in their study of aspergillosis in immunocompetent individuals, involving 23 patients, found involvement of paranasal sinuses with bony destruction and contiguous extension into the anterior cranial fossa as a common pattern. Orbital involvement was also reported in some cases. Multisite involvement was predominantly contiguous, with noncontiguous/hematogenous spread in some cases. Sites of intracranial involvement were

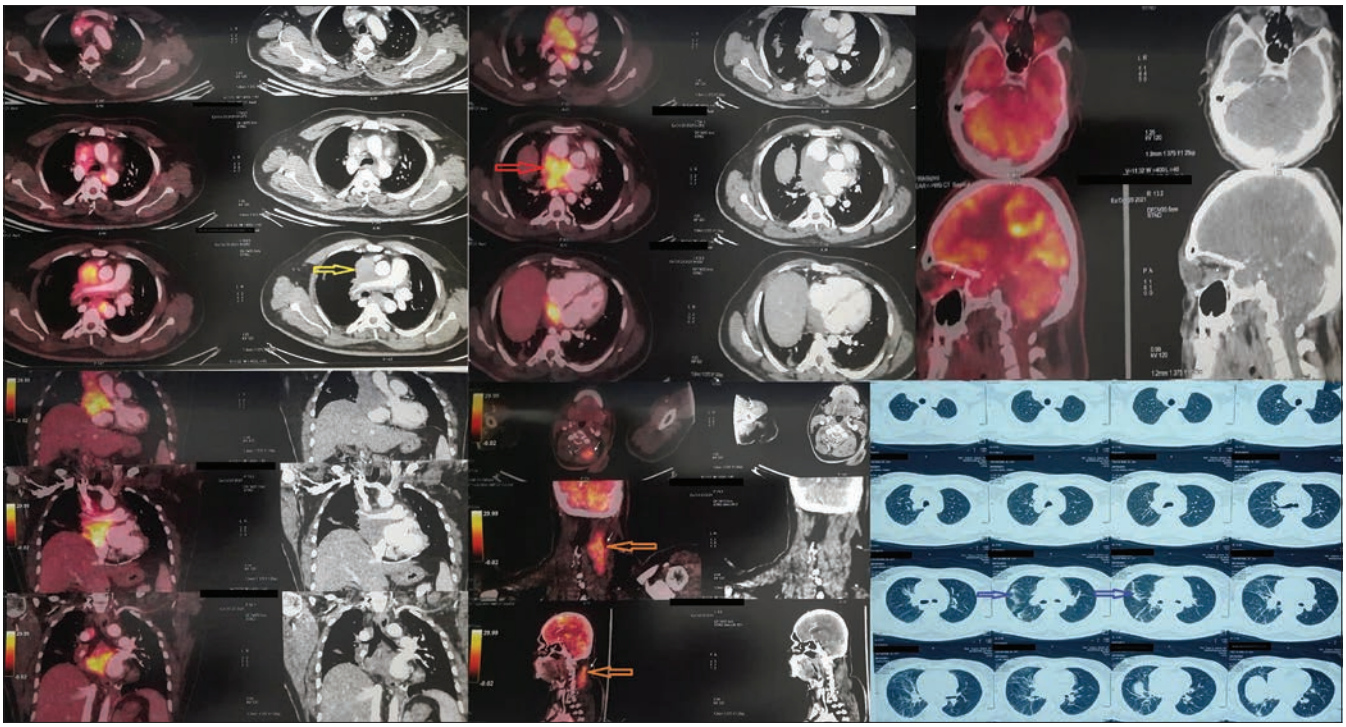


Image 4: FDG – PET scan images showing metabolically active lesions in right parietal lobe of brain, right orbit (inferior rectus muscle), and left level V lymph nodes of neck along with metabolically active mediastinal lymphadenopathy. Mediastinal lymphadenopathy are non-necrotic homogeneously enhancing type with conglomerated nodes and nodal masses. Nodal masses are also involving pericardial recesses along roots of major mediastinal vessels. There is no metabolically active lesion in lungs. Few patchy fibrotic patches are noted in right lung

parasellar and suprasellar regions along with involvement of frontal and temporal lobes. Intracranial involvement as extradural masses was a common pattern. Isolated mucosal or cerebral involvement was uncommon. On CT, paranasal sinus lesions in majority of cases were seen as dense enhancing soft tissue lesions with bone destruction. In one case, isolated mucosal thickening with poor enhancement was noted, described as a nonspecific pattern. Intracranial lesions were predominantly hyperdense on noncontrast CT and showed enhancement on post-contrast images. In patients where MRI was done, intracranial lesions were hypointense on T1 and T2W images with post-contrast enhancement. Optic nerve-sheath involvement was better seen on MRI.

In a study by Adulkar et *al.*, out of the 20 immunocompetent patients with invasive sino-orbital/naso-orbital fungal infections, 18 were found to be due to Aspergillus and 2 due to Mucor.[2] Most common presenting symptom was proptosis followed by diplopia. On CT, orbital lesions were seen as ill-defined dense soft tissue lesions with orbital fat stranding, intra- as well as extraconal involvement and varying bone destruction. Lateral rectus, inferior rectus, and inferior oblique were most commonly involved extraocular muscles. Orbital apex involvement was noted in seven cases. On MRI, lesions were T2 hypointense and T1 isointense as compared to muscle. Pansinusitis was noted in 14 patients.

Ashdown *et al.*[3] described three imaging patterns in immunocompromised patients with aspergillosis of brain and paranasal sinuses. (1) Multifocal hypodense areas on CT or T2 hyperintensity on MRI involving cortex or subcortical white matter representing embolic infarcts, which can be accompanied by hemorrhagic foci with hyperdensity on CT or T1 hyperintensity on MRI. (2) Multifocal intracerebral irregular ring enhancing lesions s/o abscesses. (3) Dural enhancement with enhancing lesions in adjoining calvaria, paranasal sinuses, or enhancement of optic-nerve sheath with enhancement in orbital fat.

Our patient had orbital disease as involvement of inferior rectus muscle with noncontiguous/hematogeneous involvement of brain parenchyma. On MRI, thickened inferior rectus muscle was T2 hyperintense with post-contrast enhancement, whereas cerebral lesions were T2 intermediate/hypointense signal intensity with post-contrast avid enhancement and surrounding T2 hyperintensity suggestive of edema. Cerebral lesions were conglomerated nodular and plaque like with irregular enhancing margins. PET-CT revealed orbital and cerebral lesions to be FDG avid, along with FDG avid cervical and mediastinal lymphadenopathy. There was

no paranasal or nasal involvement. There was no obvious bone destruction.

Ioannis Dimitrakopoulos *et al.*[4] described a case of invasive aspergillosis with involvement cerebral, orbital, and paranasal sinus involvement, in an immunocompetent individual. The lesion was seen as a soft tissue mass with contiguous involvement of left maxillary sinus, orbit and middle cranial fossa with intervening osseous destruction.

In a study by Marzolf *et al.*[5] involving 21 patients with cerebral aspergillosis, 8 patients had direct extension from paranasal sinuses and 6 patients were immunocompetent. Remaining 13 patients were having hematogenous dissemination and were immunocompromised. Cerebral lesions were in the form of abscesses and hemorrhagic lesions along with vascular complications such as aneurysms and dural venous thrombosis. Dural involvement and subdural empyema were found in patients where there was contiguous involvement from paranasal sinuses.

Huang *et al*.[6] conducted a study involving 21 patients with acute invasive fungal rhinosinusitis. Nine patients had orbital involvement and of this group 3 has brain abscesses as well. All patients with orbital involvement had diabetes mellitus, whereas malignancy was a most common predisposing factor in orbital sparing group.

Recently, covid-19 related disseminated invasive fungal infections have been reported including rhino–orbito–cerebral involvement, caused mostly by Mucor and less commonly Aspergillus.[7-9] Our patient did not have any documented history of covid-19 or covid-19 related significant morbidity.

CONCLUSION

Present case report depicts the initial presentation of hematogenous spread of aspergillosis in the form of right inferior rectus muscle palsy – The tip of ice berg with clinically silent concomitant infection of brain parenchyma, mediastinal, and cervical lymphnodes. The case report emphasizes the importance of considering fungal infection as one of the differential diagnosis of T2 hypointense neuro-parenchymal lesions in immunocompetent nondiabetic patients with no previous documented history of covid-19 infection apart from keeping other differential diagnosis of chronic infectious and noninfectious granulomatous lesions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Keratoconus comorbidity with early-onset Fuchs' endothelial dystrophy in identical twins

ABSTRACT

To report a case of keratoconus with early-onset Fuchs' endothelial corneal dystrophy (FECD) changes in identical twins. A case report. A 22-year-old female had ocular findings of corneal protrusion, Fleischer's ring, and corneal endothelium pigment dusting in both eyes. Corneal tomography showed increased corneal power and reduced thickness, and specular microscopy revealed loss of endothelial cells, the presence of a few non-confluent guttata, pleomorphism, and polymegathism in both eyes. Based on these findings, she was diagnosed as keratoconus with early grade FECD changes. Her family history revealed that she has an identical twin sister. Examination of her twin sister showed similar findings suggesting keratoconus with early grade FECD. This case report provides further evidence for the role of genetics in the development of keratoconus. Furthermore, it shows the diagnostic, monitoring, and treatment challenges due to the combination of two different diseases.

Keywords: Fuchs' endothelial corneal dystrophy, keratoconus, keratoconus in twins

INTRODUCTION

Keratoconus is a non-inflammatory, multifactorial, progressive disorder of the cornea that causes stromal thinning, which results in irregular astigmatism and vision loss.[1] The high occurrence rate in first-degree relatives and the concordance in twins suggest that keratoconus has a strong genetic component.[1] Keratoconus has been reported in association with many ocular and systemic diseases.[1] Furthermore, it has been associated coincidently with the anterior basement membrane, posterior polymorphous, and Fuchs' corneal endothelial dystrophy (FECD).[1]

The signs and symptoms of FECD typically appear in a person's 40s or 50s. FECD is a bilateral, asymmetric, non-inflammatory, progressive disease characterized by the loss of endothelial cells, a variable amount of pigment dusting on the endothelium, thickening of the Descemet's membrane, the formation of guttae, and the development of corneal edema, resulting in a significant decrease in visual acuity.[2] FECD appears to be inherited in an autosomal dominant pattern in most cases.[2] Early-onset FECD is very rare and may have a smaller corneal guttata.[2] However, a non-guttae form of FECD has been described as a variant form of the same disease.[3]

To the best of our knowledge, this is the first case report to describe the younger age presentation of keratoconus with FECD in one pair of twins, which provides further evidence for the role of genetics in the development of keratoconus.

CASE REPORT

Initial visit 23/4/2021

We present the case of a 22-year-old female (twin 1) who was diagnosed with keratoconus 1 year ago. No other previous

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medical reports were available. There was no history of trauma or infection, contact lenses, asthma, eczema, hay fever, or eye rubbing in the past. Her systemic history was unremarkable. Her family history revealed that she had an identical twin sister. On examination, her spectacle-corrected visual acuity was 6/9 with a manifest refraction of -1.25×95 OD and 6/6 with -1.0×60 OS, respectively. Slit-lamp examination revealed corneal protrusion in OD, whereas Fleischer's ring and corneal endothelium pigment dusting were visible in OU [Figure 1a, b]. Corneal tomography (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy) showed paracentral steepening OU, with corneal apex dioptric power and thinnest corneal thickness of 58.3D and 443 μm in OD, and 52.2D and 463 μm in OS, respectively [Figure 2].

Endothelial cell morphology was assessed with the SP-1P non-contact specular microscope (Topcon Co., Tokyo, Japan). Specular microscope images revealed endothelial cell loss, the presence of a few non-confluent guttata, pleomorphism, and polymegathism more severe in OD than in OS [Figure 3].

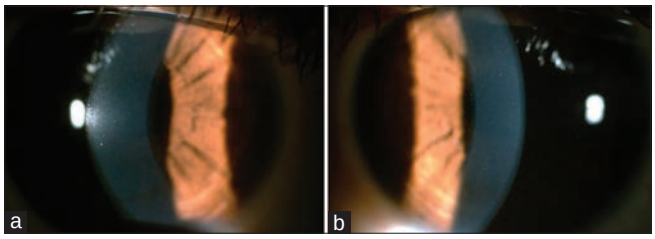


Figure 1: Twin 1 slit-lamp bio-microscopy photographs of the right (a) and left eye (b) showed corneal protrusion in the right eye, whereas Fleischer's ring and endothelial pigment dusting were visible in both eyes

Examination of the posterior segments was unremarkable. Based on the findings, she was diagnosed as having keratoconus with early grade FECD.

An ocular examination of her sister (twin 2) was also undertaken. Slit-lamp examination showed similar findings of keratoconus with early grade FECD in OU. The examination of her parents was unremarkable.

Twin 1 had more severe keratoconus than twin 2. Both the twins managed with glasses and contact lenses. Both twins explained that if keratoconus progresses further during follow-up visits, corneal collagen crosslinking would be required as a treatment option. At 9 months of follow-up, neither twin showed further progression of the disease.

DISCUSSION

The key to the diagnosis of FECD mainly includes the patterns of corneal guttae and morphology of endothelial cell mosaic; polymegathism (cell size variation) and pleomorphism (cell shape variation).[2] In the early stages of FECD, the cornea contains 1–12 or more non-confluent central guttae.[2] The endothelial cell density is the least important parameter in FECD diagnosis. A previous study found that in the presence of endothelial cell loss and guttate, neither a manual nor an automated specular microscope provides a valid endothelial cell density result.[2]

In our case, twin 1 developed symptoms at 22 years of age and keratoconus was seen with FECD. The unique aspect of these

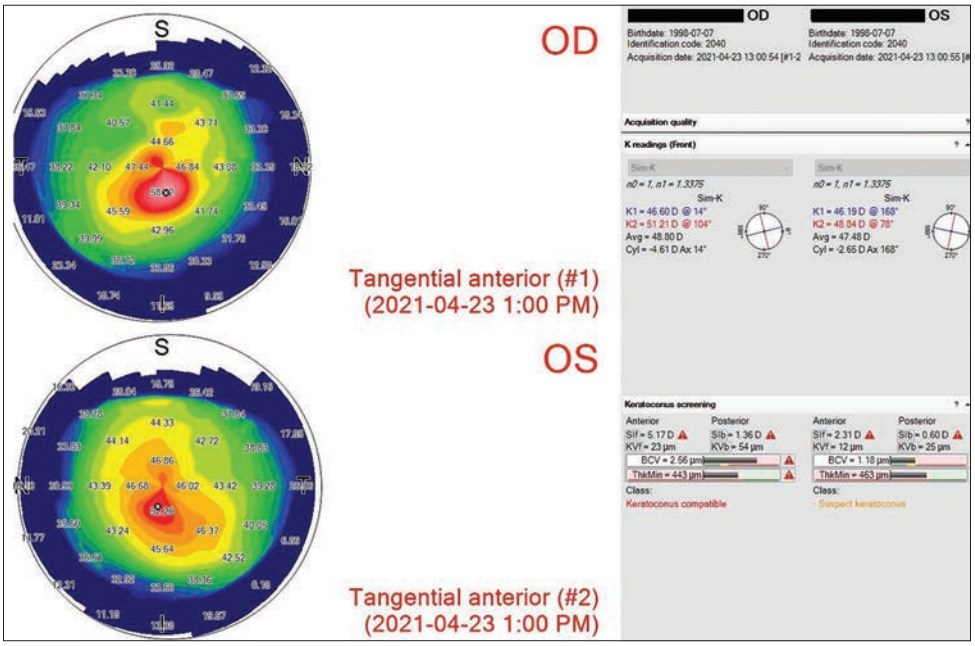


Figure 2: Twin 1 topography of right (OD) and left (OS) eyes reveals central steepening, increased corneal power, and decreased thickness showing characteristics of keratoconus in both eyes

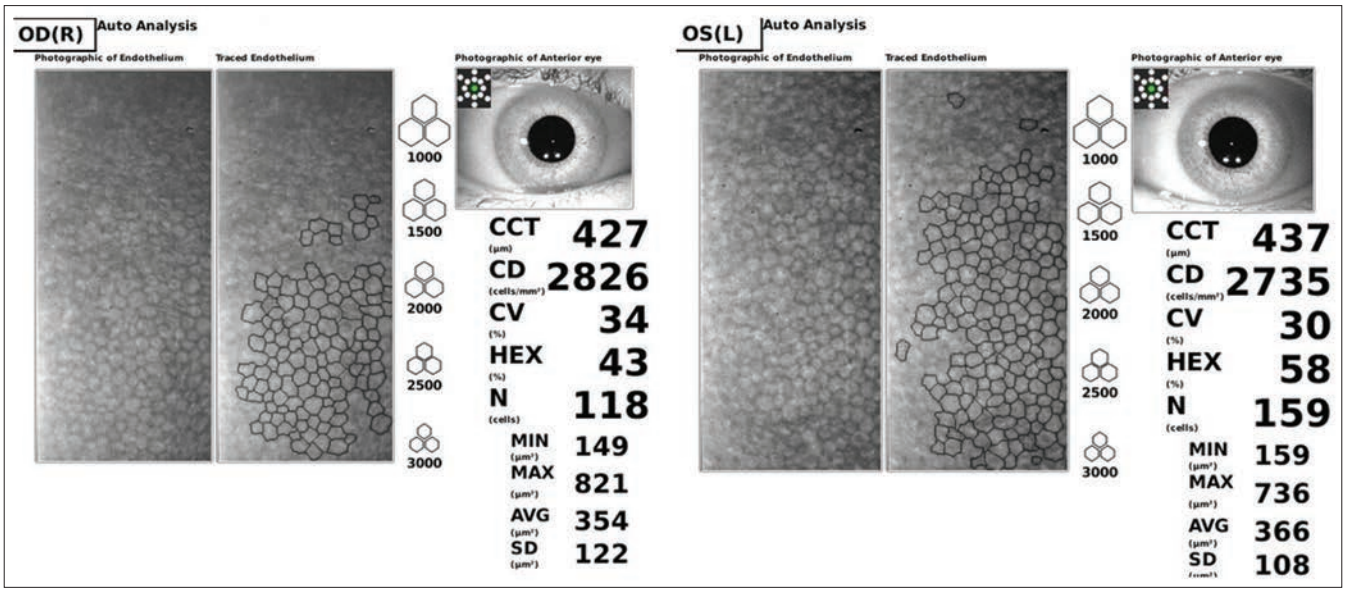


Figure 3: Twin 1 specular microscopy of the right (OD) and left eye (OS) showed endothelial cell loss, presence of a few non-confluent guttate, polymegathism, and pleomorphism. These changes were more severe in the right eye than in the left eye

cases is that these changes are seen in twins. Interestingly, more endothelial changes were observed in twins' severely affected keratoconus eyes.

Many reports have documented a coincidence between keratoconus and FECD.[4] However, in all these reports, most of the patients were older than 40 years.[4] In contrast to our study, Martone *et al*.[3] and Alnabulsi *et al*.[5] described this combination of diseases with corneal thickness greater than 600 µm in 64 and 39 years old women. The possible reason for higher thickness is the elder age presentation of the patients, which are more likely to develop corneal edema due to FECD progression. However, according to Alnabulsi *et al*.,[5] FECD may cause the appearance of pseudo-keratoconus, which is thought to be caused by Descemet's membrane protrusion caused by endothelial dysfunction. Their study found normal topographic findings after Descemet's membrane endothelial keratoplasty surgery in eyes with keratoconus and FECD. In our case, we do not know whether keratoconus is associated with FECD or whether both diseases have the same coincidence.

Keratoconus and FECD have opposite effects on corneal thickness resulting in reciprocal masking of severity and progression and progression of one by the other.[4] The treatment of these two diseases is quite different. Studies have reported that corneal collagen crosslinking may result in a reduction of endothelium cells in keratoconus eyes.[6] Considering the endothelium health and non-aggressive nature of keratoconus in both twins, delaying corneal collagen crosslinking until progression is documented is the safest option in these cases.

There are no other non-surgical treatment options available if FCED progresses. Nevertheless, in the future, intraocular injection of one adenoviral vector into the eye of patients with early-onset FECD may be used to aid in the long-term preservation of corneal endothelial density.[7]

The presence of combined dystrophy suggests that the two diseases may share a common genetic pathway. Early-onset FECD has been associated with autosomal dominant Q455K, Q455V, and L450W mutations in the gene encoding the alpha 2 subunit of collagen 8 (COL8A2).[8] However, the role of COL8A2 in the pathogenesis of keratoconus is controversial.[9] This double corneal dystrophy appears to be caused by mutations in the ZEB1 gene.[10] The increasing number of reports on this combination of diseases may prompt new genetic and molecular research to determine its pathogenesis as a new disorder.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Chondroid syringoma of medial canthus—A rare case

ABSTRACT

Chondroid syringoma of the skin is a rare, benign skin adnexal tumor, usually exhibited as a slowly growing intradermal or subcutaneous nodule, typically located in the head-and-neck region. Chondroid syringoma usually appears on the face, the medial canthus being a rare site of predilection. The diagnosis is usually made retrospectively based on histological features of the surgically excised mass, which is usually asymptomatic. We present a rare case of an 18-year-old man who presented with a painless, subcutaneous nodule medial to the medial canthus of the left eye. The diagnosis of chondroid syringoma was rendered. To the best of our knowledge, only one case of chondroid syringoma of the medial canthus has been documented in the literature. A histopathological examination is mandatory for arriving at the diagnosis. It should be considered in the differential diagnosis of all the slowly growing nodular lesions in the face.

Keywords: Chondroid syringoma, medial canthus swelling, benign skin tumours

CASE REPORT

An 18-year-old male presented to the Ophthalmology Department of HIMS, Barabanki, with a left-sided subcutaneous nodule inferior to the medial canthus for one year [Figure 1]. The mass was approximately 12.4 × 7.4 mm, painless, progressive in nature, non-tender, and mobile with fixity to the overlying skin but not fixed to the underlying structures, firm consistency, and smooth surface. The overlying skin was normal. The transillumination test is negative.

On examination, his vitals were within normal limits, and vision tests were normal.

Syringing shows a patent nasolacrimal duct.

INVESTIGATIONS

The patient was sent for radiological investigations to know the extent of the swelling. CT orbit of the left eye was done. The findings of which suggested:

Relatively defined soft tissue swelling was seen in the region of inferior to medial canthus of the left eye, m = 12.4 × 7.4 mm. The lesion is not seen as causing any scalloping/erosion of underlying nasal bone.

Impression: Soft tissue swelling in the region of the inferior to the medial canthus.



Figure 1: Showing pre-op swelling at medial canthus on left side

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Figure 2: Showing excised tumour during surgery

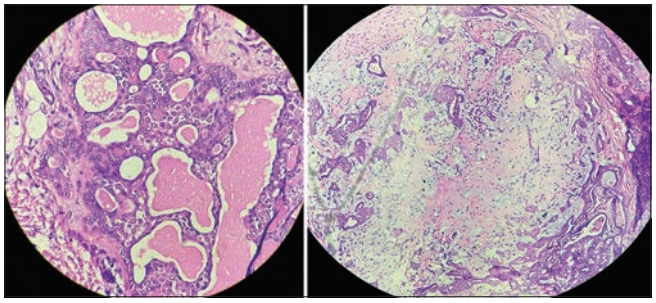


Figure 3: Showing histological picture of chondroid syringoma depicting dual layered epithelial cells with outer layers flattened and arranged in ducts and sheets



Figure 4: Showing immediate post-op and 1 week after post-op depicting no recurrence of the swelling

Other blood investigations (CBC, RBS, and viral markers) were in the normal range.

SURGERY

Local anesthetic (2% lignocaine with bupivacaine) was instilled circumferentially around the swelling.

Around 8 mm incision was given inferiorly to the medial canthus region.

The skin was separated, following which orbicularis fibers were separated, and blunt dissection was done, after which the soft tissue mass was exposed.

Complete excision of the mass [Figure 2] was done under local anesthesia and sent for histopathological examination.

The muscle layer is sutured with a 6'0" Vicryl suture, and the skin is closed with a 6'0" Ethilon suture.

The patient was called for a follow-up after seven days for suture removal.

Histopathological findings

Histopathological examination (HPE) findings showed dual-layered epithelial cells with outer layers flattened and arranged in ducts and sheets. These elements are dispersed within a mesenchyme-like background of loose myxoid tissue containing islands of chondroid tissue within these epithelial cells' cystic spaces containing eosinophilic fluid seen [Figure 3].

No features suspicious of malignancy, such as cytological atypia, cellular pleomorphism or dysplasia, mitotic figures, infiltrative margins, satellite tumor nodules, or tumor necrosis, were found on histology. The diagnosis of chondroid syringoma (benign mixed tumor of the skin) was rendered.

There has been no recurrence of the same in the follow-up, and the patient is doing well [Figure 4].

DISCUSSION

Chondroid syringoma is a benign mixed tumor characterized by sweat gland elements in a cartilaginous stroma. This rare tumor accounts for only 0.01% of all primary skin tumors and occurs only rarely in the periorbital region.[1] Usually between 0.5 cm and 3.0 cm, the risk of malignancy increases in chondroid syringoma greater than 3.0 cm in size. Chondroid syringoma is a benign neoplasia named because it is a proliferation of tubular and ductular eccrine or apocrine epithelium similar to that of a syringoma, mixed with a characteristic chondroid stromal matrix. Chondroid syringoma is a rare mixed tumor of sweat gland origin first described in 1859 by Bilroth as a tumor type similar to a benign mixed tumor of salivary glands.[2] Hirsch and Hellwig later classified this tumor type as chondroid syringoma in 1961 due to the presence of sweat gland elements in a cartilaginous stroma.[3]

The tumor is composed of tubular structures lined by a double layer of epithelial cells embedded in a mucoid stroma, often with areas of chondroid metaplasia. It occurs most frequently in the head and neck; the common sites are the scalp, cheek, nose, upper lip, chin, and forehead. Less commonly, this tumor can involve the hand, foot, axillary region, abdomen, penis, vulva, and scrotum. Headington has described two types of chondroid syringomas depending on the morphological picture. The present case was chondroid syringoma with tubular branching lumina. In general, the tubular structures are highly suggestive of eccrine differentiation. The other variety is chondroid syringoma with small, tubular lumina in which glands are lined by a single layer of flat epithelial cells. The tumor can differentiate either to eccrine or apocrine elements, and very rarely, it can undergo malignant change with widespread metastases. The malignant transformation is more common in young females and has a predilection for occurring in the trunk and extremities.[4] Tyagi *et al*., in their study of 207 eyelid tumors, had one case of chondroid syringoma with an incidence of 0.48% in their series.[5] Malignant transformation is rare, but cases have been encountered mostly in women and are more common in the extremities. Tumors >3 cm in size have a greater likelihood of malignancy.[6] Usually, the patient does not show any symptoms, and excision is done for a cosmetic reason only. The diagnosis is usually made retrospectively based on the histological findings of the excised lesion. The conditions that may be included in the clinical differential diagnoses are implantation dermoid, sebaceous cyst, compound nevus, clear cell hidradenoma, cystic basal cell carcinoma, neurofibroma, and dermatofibroma. Most of the above-mentioned entities present as a subcutaneous nodule with normal overlying skin with the exception of basal cell carcinoma, which starts as a small brownish-red nodule with translucent color and shiny surface showing a network of capillaries, and later become ulcerated with a well-defined, hard, and raised edge with a beaded appearance. Chondroid syringoma may metastasize despite bland cytological features, lacking mitoses, or marked nuclear pleomorphism. Excessive amounts of mucoid matrix and poorly differentiated chondroid components serve as important indicators of the malignancy and metastatic potential of the tumor. The treatment of choice is a local complete surgical excision because of the risk of malignancy. If the tumor has been completely excised and is benign, long-term follow-up is not indicated. Follow-up is indicated only if the excision is incomplete, which may recur or transform into malignancy, which has been very rarely documented in the literature. Other methods of treatment are electrodessication, dermabrasion, and vaporization with argon or CO_2 laser. For malignant lesions, the initial treatment modality is aggressive surgery followed by adjuvant radiotherapy, with or without chemotherapy.

CONCLUSION

Chondroid syringoma is a rare, slow-growing, non-ulcerated, and painless mixed tumor of the skin, usually occurring in the head-and-neck regions. Clinicians should be aware of these tumors since they are very rare in occurrence and can be misdiagnosed. It should be considered in the differential diagnosis of all the slowly growing nodular lesions in the face. This case is being reported for its rarity, its occurrence in young patients, and the need to keep this rare entity as a differential diagnosis of eyelid tumors.

Declaration of patient consent

All appropriate patient consent forms were taken. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Endophthalmitis following vitrectomy for malignant glaucoma: Multidrug-resistant *Klebsiella pneumoniae*

ABSTRACT

The purpose of this case report is to present a case of acute-onset postoperative endophthalmitis, caused by multidrug-resistant (MDR) *Klebsiella pneumonia*, following pars plana vitrectomy for malignant glaucoma. A 52-year-old male patient underwent elective phacoemulsification cataract surgery with intraocular lens implantation in the right eye. Two weeks later, the patient presented with a diminution of vision and clinical features suggestive of malignant glaucoma. With no response to conventional treatment, pars plana vitrectomy was done. Acute-onset postoperative endophthalmitis developed, with severe intraocular inflammation, caused by MDR *Klebsiella pneumoniae*. The isolates demonstrated sensitivity to polymyxins and tigecycline only. Intravitreal colistin (0.1 mg/0.1 mL) was administered. The response was satisfactory and the vision could be salvaged. At 2 months follow-up a visual acuity of 20/50 was recorded. This is a rare case report of acute-onset postoperative endophthalmitis due to MDR *Klebsiella* following pars plana vitrectomy. With timely intervention, the patient came out of two difficult situations of malignant glaucoma and MDR endophthalmitis with a reasonably good visual recovery.

Keywords: Endophthalmitis, malignant glaucoma, polymyxins, vitrectomy

INTRODUCTION

Malignant glaucoma, also known as aqueous misdirection syndrome, is characterized by elevated intraocular pressure (IOP) and uniform flattening of the anterior chamber in the presence of a patent peripheral iridotomy and normal posterior segment anatomy. Malignant glaucoma usually occurs after filtration surgery done for angle-closure glaucoma but is also reported following cataract surgery, YAG iridotomy, and capsulotomy. The pathophysiology of malignant glaucoma is poorly understood but is thought to be due to an alteration in the anatomical relationships of the ciliary body, lens, and anterior vitreous face. A misdirected flow causes accumulation of aqueous behind a posterior vitreous detachment causing a secondary forward shift of lens-iris diaphragm closing the angle of the anterior chamber. The management of this relatively rare condition has usually been challenging. The standard initial treatment is medical therapy with hyperosmotic agents, aqueous suppressants, and cycloplegics. If the pseudophakic eye does not respond to the medical therapy, then YAG iridotomy, capsulotomy, anterior hyaloidotomy, and parsplana vitrectomy are the other means to tackle the situation.[1,2]

Acute-onset endophthalmitis, a potentially catastrophic disease can be a consequence of intraocular procedures, trauma, or an endogenous source. Acute postoperative endophthalmitis, the most common category, is characterized by severe inflammation of ocular tissues and fluids. This may occur following cataract surgery, intravitreal injections, and rarely parsplana vitrectomy. The reported incidence

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of postcataract surgery endophthalmitis is 0.04–4%, and the incidence following parsplana vitrectomy (PPV) is even lower, around 0.02–0.05%. Gram-positive bacteria are more commonly isolated than Gram-negative bacteria from acute-onset endophthalmitis.[3]

We present a case of routine cataract surgery with postoperative malignant glaucoma, requiring parsplana vitrectomy developing postvitrectomy endophthalmitis. The causative organism was determined to be multidrug-resistant (MDR) *Klebsiella pneumoniae*. The entire clinical narrative has many critical moments till a reasonably satisfactory outcome.

FINDINGS

A 52-year-old male patient had right eye cataract surgery 2 months back. During cortical aspiration, small PC rent was detected, 1 mm in size (paracentral, nasally), but with no vitreous disturbance. The anterior hyaloid face appeared intact. A rigid PMMA IOL was placed in the bag. The immediate postoperative period was satisfactory with a clear cornea, round and reacting pupil, and PC IOL in the bag. Visual acuity was 6/12.

Two weeks later, the patient presented with a marked diminution of vision and severe pain in the right eye. On examination, visual acuity in the right eye was hand movements, corneal epithelial edema, almost closed anterior chamber, mid-dilated pupil not reacting to light, and PC IOL in position [Figure 1]. Fundus view was hazy due to corneal edema and details were not clear. Intraocular pressure was 45 mmHg. B-scan showed a clear vitreous with normal RCS complex. A presumptive diagnosis of malignant glaucoma was thought of and IOP-lowering treatment was started, with cycloplegics (Homatropine). Intravenous Mannitol was also given; 100 mL of 15% solution over 30 minutes period. Dorzolamide and Timolol eye drops 12th hourly and tablet Acetazolamide 250 mg 8th hourly was continued. There was no response for 48 hours with IOP being 60 mmHg. Peripheral Yag laser iridotomy was done 48 hours later. There was no improvement. Laser capsulotomy and hyaloidotomy were not attempted. A pars plana anterior vitrectomy was contemplated.

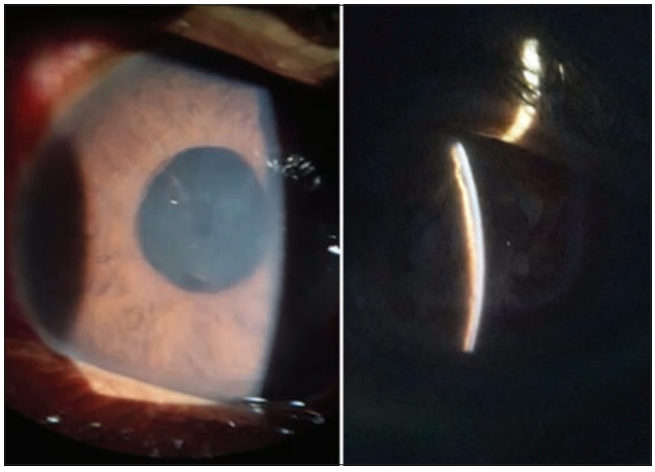


Figure 1: Slit lamp photograph of the right eye showing shallow anterior chamber with corneal epithelial edema

Pars plana vitrectomy was done with the removal of the anterior hyaloid face and anterior vitreous to eliminate the blockade and aqueous misdirection. Iris movement and deepening of the anterior chamber were seen. Reformation of the anterior chamber was achieved. All sclerotomy sites were checked for leakage after the removal of the cannulas. In the immediate postoperative period, marked AC reaction with hypopyon 1 mm was seen, and IOP was raised to 35 mmHg. The patient was diagnosed with acute postoperative endophthalmitis. Anterior chamber wash was done and AC aspirate and vitreous tap were taken for culture and sensitivity and empirically intravitreal Vancomycin (1 mg/0.1 mL) and Ceftazidime (2.25 mg/0.1 mL) were given. Immediate Gram's stain and KOH mount did not show any organisms. Forty-eight hours later, the vitreous tap culture report showed multidrug-resistant (MDR) *Klebsiella pneumonia,* grown on a blood agar culture medium [Figure 2]. The anterior chamber aspirate was sterile. The organism was resistant to all antibiotics, except Polymyxins and Tigecycline. By then the anterior chamber reaction was severe with a thick, yellow-brown hypopyon >2 mm, and IOP was 38 mmHg. B-scan showed fine to coarse vitreous opacities with choroidal thickening [Figure 3] The penetrating instruments, vitreous cutters, endoillumination pipes, and infusion cannulas were also cultured but there was no growth.

The patient underwent anterior chamber wash followed by 23 G pars plana vitrectomy and intravitreal colistin (0.1 mg / 0.1 ml) was administered. Topical Colistin (reconstituted to



Figure 2: *Klebsiella pneumoniae* on Columbia sheep blood agar. Mucoid colonies after 24 hours of cultivation in an aerobic atmosphere, 37°C. Microscopic picture of Gram-negative short, plumb rod-shaped bacilli

0.19%), Prednisolone Acetate, and Homatropine eye drops were continued. There was an improvement, but a persistent mild AC reaction and fluctuating IOPs were observed. Repeat B-scans showed clear vitreous with normal RCS. Seventy-two hours later, the cornea was clear with mild AC reaction and persistent mild pigment dispersion and grayish-brown membrane in the pupillary area. The fundus seen hazily showed a clear vitreous and flat retina. IOP was 8 mmHg. Topical Colistin, Prednisolone Acetate, and Homatropine are continued with systemic steroids. AC wash (sticky exudative material was aspirated) with intravitreal Colistin 0.1/0.1 mL was repeated. Subsequently, 2 days later cornea was clear, with no AC reaction. Visual acuity was counting fingers at 4 meters. A week later, the condition had improved with no conjunctival congestion, mild corneal stromal haze, mild pigmentary dispersion in AC, Iris somewhat muddy, pupil round, peripheral Iridotomy intact, PC IOL in position. The fundus showed mildly hazy media with a retina flat. IOP was 19 mmHg.

The patient was in good health and was not suffering from any known systemic illness. Yet, a thorough systemic evaluation was done to look for any focus of infection. The patient was last seen 2 months after surgery and had a visual acuity of 20/50, with a normal anterior segment and normal fundus [Figure 4].

DISCUSSION

Malignant glaucoma occurs in 2–4% of eyes undergoing surgery for angle-closure glaucoma, trabeculectomy, cataract surgery, glaucoma drainage implantation, and argon laser photocoagulation.[1] Vitrectomy surgery leads to the resolution of malignant glaucoma in 65–90% of pseudophakic eyes. Endophthalmitis following PPV is of relatively uncommon occurrence compared to cataract surgery and intravitreal injections. The potential predisposing causes for endophthalmitis following small gauge vitrectomy include immunosuppression, preoperative corticosteroids, inadequate wound closure, postoperative hypotony, and vitreous incarceration at the sclerotomy site. Immediately post-vitrectomy, the sclerotomy sites were inspected and found to be stable with no vitreous incarceration. It is a usual practice of the surgeon to put a single 8-0 vicryl suture at sclerotomies. There was no postoperative hypotony.

Multiple studies have reported a variety of organisms in post-PPV endophthalmitis. The most commonly reported organism is coagulase-negative staphylococci.[4] To the best of our knowledge, this is the first reported case of post-PPV endophthalmitis caused by MDR *Klebsiella*. *Klebsiella* species are recognized as an important cause of endogenous endophthalmitis. Reported risk factors are liver abscesses, immune compromise, and diabetes mellitus.[5,6] Visual prognosis in acute postoperative endophthalmitis is often guarded, with only about 30% of cases recovering visual acuity better than 20/40.[7] Visual prognosis declines further in the presence of multidrug-resistant strains due to limited treatment options. *Klebsiella pneumonia*-associated endophthalmitis has a poor visual prognosis, and multidrug-resistant strains pose a bigger challenge due to the virulent nature of the organism. MDR strains of *Klebsiella* species are resistant to conventional antibiotics like cephalosporins, aminoglycosides, and tetracyclines due to the presence of plasmids. This necessitates the use of unconventional antibiotics like polymyxin B, colistin, and tigecycline.[8] We have used only the intravitreal route to administer colistin. There is a limited role for intravenously administered colistin for gram-negative endophthalmitis because colistin does not reach therapeutically relevant levels in aqueous and vitreous.[9] There are few reported cases of successful use of intravitreal colistin in gram-negative endophthalmitis. Samant and Ramugade have successfully

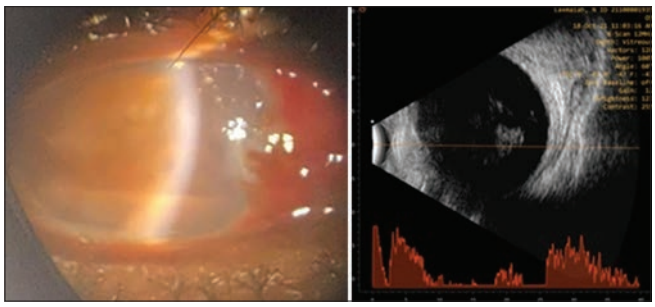


Figure 3: Marked conjunctival injection, corneal epithelial edema, and the anterior chamber has a severe fibrinous and exudative reaction with 30% hypopyon. B-scan shows choroidal thickening and vitreous opacities

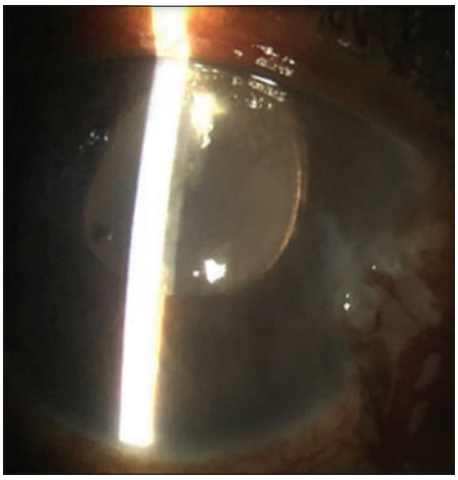


Figure 4: Slit lamp photograph in the postoperative period, 2 months after PPV and IVAB, shows corneal clarity, clear anterior chamber, and good red glow

used intravitreal colistin to salvage eight eyes of MDR *Pseudomonas aeruginosa* endophthalmitis.[10] Dogra, Mohit *et al.*[11] reported successful use in a 35-year-old male who developed endogenous MDR *Klebsiella* endophthalmitis after drainage of a pancreatic cyst.

CONCLUSIONS

Malignant glaucoma necessitating pars plana vitrectomy, developing MDR *Klebsiella* endophthalmitis warranted the use of an old class of cyclic polypeptide antibiotics, polymyxins, with a successful outcome. With the emergence of multidrug-resistant organisms, unconventional antibiotics can be considered for endophthalmitis. Any retinal toxicity due to colistin needs to be ascertained in the follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Isolated foveal hypoplasia: A case series

ABSTRACT

Foveal hypoplasia is a well-known condition characterized by an absent or abnormal foveomacular reflex. It may occur in isolation or in association with aniridia, albinism, achromatopsia, microphthalmos, and other anterior segment anomalies. The clinical diagnosis might often be missed due to the subtle nature of findings. We describe five cases of two families with isolated foveal hypoplasia. The presence of nystagmus and unexplained poor vision in children without features of retinal dystrophies should raise a suspicion of isolated foveal hypoplasia. Detailed and careful fundus examination, especially the foveal area, helps in diagnosing the same.

Keywords: Congenital nystagmus, foveal hypoplasia, low vision, optical coherence tomography

INTRODUCTION

Nystagmus with low vision in children is a diagnostic challenge. Retinal dystrophies either as rod-cone or cone-rod dystrophy, Leber's congenital amaurosis, macular dystrophies, and idiopathic infantile nystagmus are most commonly thought of in this setting. However, foveal hypoplasia as an entity may also have similar presenting features.

Foveal hypoplasia is a condition in which the fovea is underdeveloped and is characterized by the absence of foveal pigmentation and/or the foveal avascular zone (FAZ). It has ill-defined foveomacular area, and presence of capillaries running abnormally close or traversing the macula.[1-4]

It is most commonly seen in association with other eye conditions such as aniridia, albinism, achromatopsia, microphthalmos, retinopathy of prematurity (ROP), myopia, and incontinentia pigmenti (IP). Further foveal hypoplasia in association with optic-nerve-decussation defects and anterior segment dysgenesis known as FHONDA is also reported.[1-5]

Isolated foveal hypoplasia (IFH) is a rarer disorder, with similar clinical findings in the fovea. The characteristic findings of patients with IFH are nystagmus, poor visual acuity, absent or abnormal maculofoveal reflexes on ophthalmoscopy, and variable and incomplete filtering of the choroidal fluorescence in the macular area on fluorescein angiography.

No single hereditary pattern has been established for patients with IFH. Reported cases include patients with autosomal dominant and autosomal recessive inheritance patterns as well as sporadic cases.[6-10] Isolated FH is most commonly sporadic, but the association with PAX6 missense mutation was identified.[8] The molecular basis of isolated autosomal recessive foveal hypoplasia is yet unknown; however, a homozygous SLC38A8 mutation has been reported.

Foveal hypoplasia and optic nerve misrouting are developmental defects of the visual pathway not only co-occur in connection with albinism, but these defects can occur independently of albinism in people with recessive mutations in the putative glutamine transporter gene SLC38A8.[6,9]

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However, IFH is reported rarely. We report two Indian families with affected members having IFH.

CASE REPORT

Family 1

Family 1 presented to us with three children complaining of reduced vision and nystagmus since birth. They were born to a grade 2 consanguineous marriage. The children in question included a pair of fraternal twins (one boy and one girl) 3 years old and the younger daughter aged 1.5 years old. All three had history of delayed milestones following normal delivery. Systemic and neurological consultation was sought and found to be normal.

All children fixated and followed light. They had small face turn with exotropia for near.

All of them had pendular horizontal nystagmus with a small jerky component in both eyes. There were no transillumination defects and lens was normal.

Indirect ophthalmoscopy showed absent foveal reflex. Clinical diagnosis of IFH was made and advised OCT. OCT was obtainable in one of the twins with difficulty. Swept-source optical coherence tomography (OCT) showed grade 3 foveal hypoplasia with absence of extrusion of plexiform layers, absence of foveal pit, and absent outer-segment lengthening. Outer nuclear layer widening was present [Figures 1 and 2].

Family 2

The next family presented to us with two children, aged 13 and 8 years, with complaints of decreased vision and nystagmus. They were born to a grade 3 consanguineous marriage.

The younger child adopted a chin-down posture. Both children had exotropia. They had a pendular nystagmus with left beating jerk component. Both children had compound hyperopic astigmatism with a BCVA of 6/24 (OU) N12 in the elder child and 6/18 (OU) with single optotype; N12 in the younger child.

The anterior segment examination was normal. Fundus examination showed absent foveal reflexes in both eyes, with few retinal capillaries running abnormally close to the presumed foveal area [Figure 3a and 3b]. OCT showed grade 3 foveal hypoplasia.

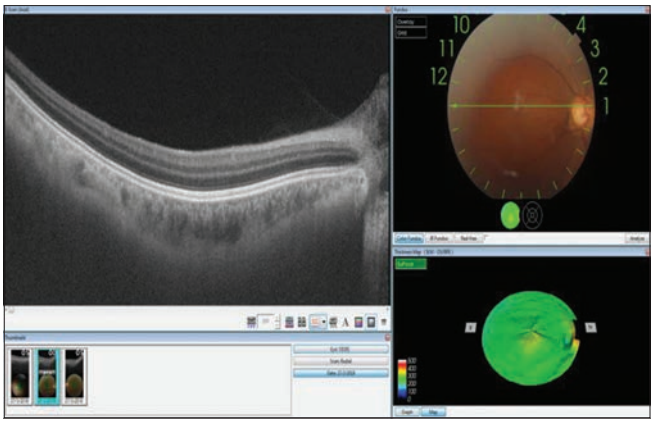


Figure 1: Optical coherence tomographic image of right eye showing absent foveal pit, with absence of extrusion of plexiform layers, and absent outer-segment lengthening suggestive of grade 3 foveal hypoplasia of the 3-year-old boy of family 1

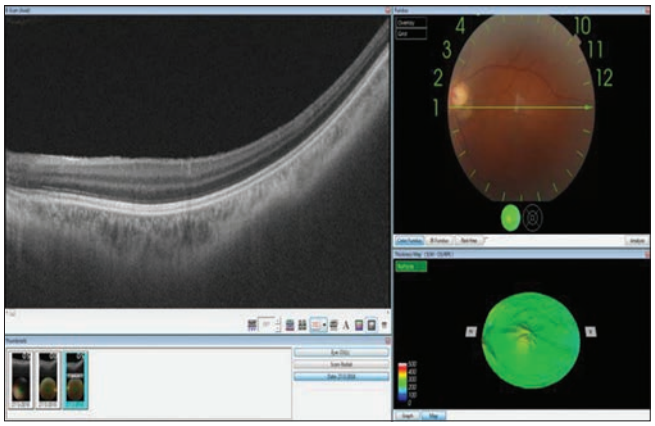


Figure 2: Optical coherence tomographic image of left eye showing absent foveal pit, with absence of extrusion of plexiform layers, and absent outer-segment lengthening suggestive of grade 3 foveal hypoplasia of the 3-year-old boy of family 1

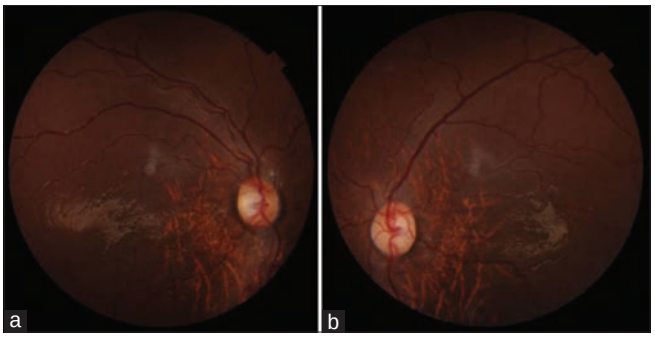


Figure 3: (a and b) Color fundus photograph showing absent foveal reflex and normal vasculature in right and left eye of the 13-year-old boy of family 2

DISCUSSION

Foveal hypoplasia is thought to be the result of the failure of formation of FAZ. Foveal hypoplasia as a cause of low vision and nystagmus is well documented. It may occur in isolation or in association with other conditions such as aniridia, albinism, achromatopsia, microphthalmos, ROP, myopia, and IP.[1-6] However, IFH is a rare entity.

IFH has been described as early as 1976 by Curran and Robb.[1]

There are several case reports of IFH with overlapping anterior segment findings. Thomas *et al*. described 14 patients with nonfamilial IFH, absent *PAX6* mutation, a mean best-corrected visual acuity of 0.2, logMAR, and grade 1 foveal hypoplasia on SD-OCT imaging. They identified four grades of FH by OCT imaging, from grade 1, showing only a shallow foveal pit, to grade 4 with features that include complete absence of the foveal pit. They correlated the structural grading to the visual acuity in these patients ($P < 0.0001$),[7] thus explaining variable vision findings in these patients.

Saffra *et al*. described five affected individuals with familial IFH with an autosomal recessive inheritance pattern and absent *PAX6* mutation.[10]

In our series, we describe five children of two families presenting with low vision and nystagmus since birth who on examination had foveal hypoplasia. There was no associated anterior segment dysgenesis and the IOP was normal. OCT confirmed the diagnosis, hence isolated in occurrence. Further, the occurrence of foveal hypoplasia in almost all siblings in both the families suggests a familial etiology. In our situation, due to the sparing of the previous generation, an autosomal recessive type of inheritance is likely. Genetic testing could not be done for the families due to financial constraints.

The fundal findings in IFH are very subtle and difficult to detect, because of the accompanying nystagmus. Foveal hypoplasia could, therefore, be an underdiagnosed rather than an uncommon entity. OCT is useful tool for the diagnosis.

CONCLUSION

The presence of nystagmus and poor vision in children and infants, without any other ocular findings, should raise a suspicion of IFH and should prompt the ophthalmologist to carry out a thorough fundal examination of the maculofoveal area in detail.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Harnessing the power of artificial intelligence for glaucoma diagnosis and treatment

ABSTRACT

Artificial intelligence (AI) has great potential for diagnosing and managing glaucoma, a disease that causes irreversible vision loss. Early detection is paramount to prevent visual field loss. AI algorithms demonstrate promising capabilities in analyzing various glaucoma investigations. In analyzing retinal fundus photographs, AI achieves high accuracy in detecting glaucomatous optic nerve cupping, a hallmark feature. AI can also analyze optical coherence tomography (OCT) images of the retinal nerve fiber layer(RNFL) and ganglion cell complex, identifying structural changes indicative of glaucoma and also Anterior Segment OCT(AS-OCT) for angle closure disease. OCT interpretation may even be extended to diagnose early features of systemic neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease. Furthermore, AI can assist in interpreting visual field (VF) tests, including predicting future VF loss patterns for the next 5 years. The ability of AI to integrate data from multiple modalities, including fundus photographs, Intra Ocular Pressure(IOP) measurements, RNFL OCT, AS-OCT, and VF tests, paves the way for a more comprehensive glaucoma assessment. This approach has the potential to revolutionize ophthalmology by enabling teleophthalmology and facilitating the development of personalized treatment plans. However, the authors emphasize the crucial role of human judgement and oversight in interpreting AI-generated results. Ultimately, ophthalmologists must make the final decisions regarding diagnosis and treatment strategies.

Keywords: Artificial intelligence, eye pressure, forecasting visual fields, glaucoma, glaucoma AI, machine learning, normal tension glaucoma, OCT, perimetry, predicting field progression, target IOP, triggerfish

INTRODUCTION

Glaucoma is an eye disease, which is known as the silent thief of sight and for good reason. With current technologies, it is impossible to recover vision lost due to glaucoma, which makes it all the more important to diagnose glaucoma early from whatever information is available, monitor progression before it causes significant damage, and plan ideal treatment so that we can achieve a balance between the clinical, social and economic factors affecting it.

Practical decisions on treatment and follow-up would depend on not only the intraocular pressure, visual fields, optical coherence tomography (OCT), gonioscopy, corneal thickness but also on systemic conditions, side effects, patient affordability, occupation, age, and sociocultural factors. Glaucoma is not just a clinical disease, but truly a patho-physio-psycho-socio economic disease as mentioned by Dr Karim Damji and Dr R Venkatesh.

Artificial intelligence (AI) has a major emerging role in ophthalmology and glaucoma.[1–14] AI promises to help sort through the Big Data[15] of glaucoma investigations to detect early glaucoma, pre-perimetric glaucoma from perimetry, progression

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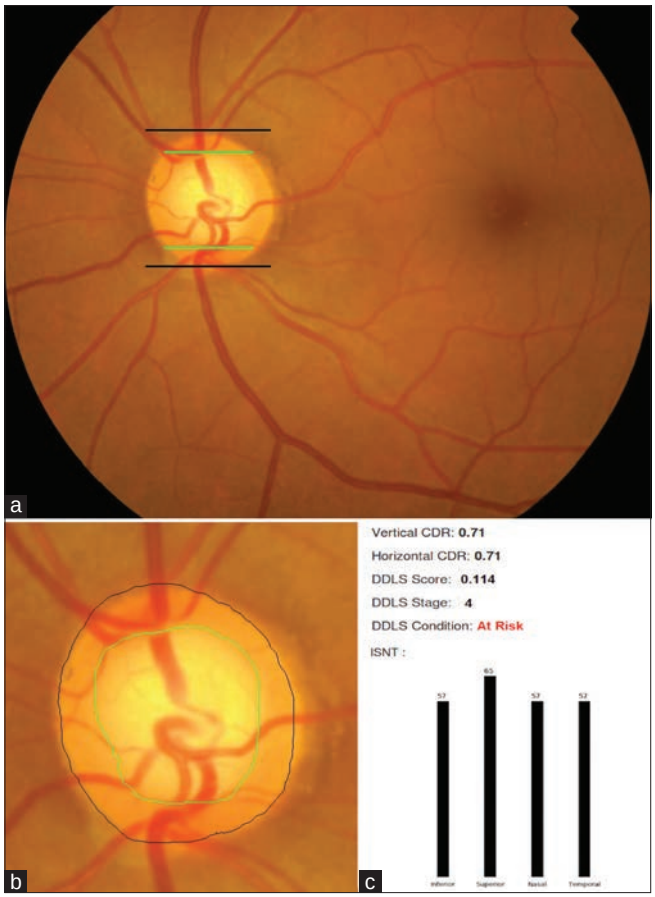


Figure 1: AI segmented image of glaucomatous optic disc showing (a) vertical cup and disc margins, (b) 360-degree cup and disc margins, (c) disc parameters including the cup disc ratio, DDLS score, and ISNT (inferior, superior, nasal, temporal) rims

not detectable from conventional progression analysis and predict future visual field for even the next 5 years. Figure 1 shows a trained AI algorithm's evaluation of a retinal fundus photograph for glaucoma. Figure 2 shows retinal images imagined by Google Gemini when asked to create a retinal image of a glaucomatous fundus. Both ChatGPTs were unable to generate a retina image in spite of multiple similar custom prompts. Note that this Gemini-generated image does not show a glaucomatous disc and seems more like an artist's watercolor painting of a retina photograph complete with the notch in the top-right corner. My explanation is that Gemini, being a large-language model not trained to evaluate retinal images, does not yet understand what features in a fundus photograph (cupping and other disc changes) most represent glaucoma. Figure 3 shows an image generated by Microsoft Copilot using similar prompts as for Gemini, but the result is further away from what a real fundus image should look like. These generative adversarial network (GAN) AIs are rapidly evolving, and we shall look at AIs that can produce good fake fundus photography, computed tomography (CT), magnetic resonance imaging (MRI), and other imaging modalities in a later article.



Figure 2: AI-generated image of "glaucomatous" retinal fundus as imagined by Google Gemini (image generated from custom prompts in June 2024). Note that this Gemini-generated image does not show a glaucomatous disc and seems more like an artist's watercolor painting of a cherry red spot fundus photograph, the illusion of a fundus photograph enhanced with the notch in the top-right corner

Several researchers have looked at various aspects of using AI in glaucoma diagnosis, prognosis, progression detection, and prediction of the future.

OPTIC DISC AND FUNDUS EVALUATION

Many of the engineering student projects are in the medical field, and more so in ophthalmology, the most popular being the detection of glaucomatous cupping from fundus photographs, along with diabetic retinopathy grading. While some are very basic algorithms that do a segmentation of the cup and disc and evaluate the cup-disc ratio, others look at various other signs of glaucomatous optic discs as well.

Li *et al.*[16] demonstrated a deep learning algorithm that detected referable glaucomatous optic neuropathy (GON) with high sensitivity and specificity but it was confused by physiological cupping and pathological myopia. Fei Li *et al.* developed an algorithm using 17,497 color fundus photographs from 9346 patients that could predict and stratify the risk on glaucoma onset and progression. Pegasus (Visulytix Ltd., London UK) artificial intelligence, which can be accessed free through the Orbis Cybersight Consult Platform, was demonstrated to outperform 5 out of 6 ophthalmologists in a study by Al-Aswad *et al.*[17] Another group led by Cerentini *et al.*[18] used GoogLeNet deep learning network for detecting glaucomatous cupping in fundus photos. Haleem *et al.*[19] used automated boundary detection and Thompson *et al.*[20] measured NRR loss.

Ajitha, Akkara, and Judy trained a 13-layer convolutional neural network implemented in Google Colab with fundus

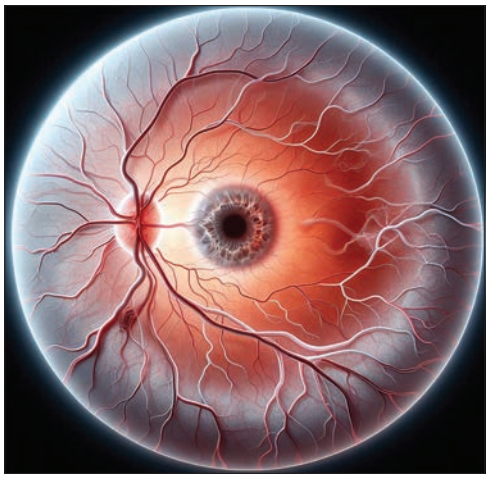


Figure 3: AI-generated image of "glaucomatous" retinal fundus as imagined by Microsoft Designer (Part of Microsoft Copilot) powered by DALL-E 3 (image generated from similar custom prompts as Figure 2) Designer created an iris and pupil at the macula and a stylized 3D retina unlike what Gemini created. Note that the designer neglected to put a notch in the top-right corner of the "fundus photo"

photographs and demonstrated very good accuracy, sensitivity, specificity, and precision in detecting glaucomatous cupping.[21] RIA-G, from Kalpah Innovations, a software for automated analysis of optic nerve head photographs, was evaluated by Singh *et al.*[22]

Lee *et al.*[23] proposed a software based on a novel deep learning classifier that that can automatically detect RNFL defects from red-free fundus photographs. Hung *et al.*[24] showed that even though red-free images were better at detecting disc hemorrhages and wedge RNFL defects, color fundus images had a significant advantage in the ternary classification of glaucoma with deep learning systems. Another study by Lee *et al.*[25] demonstrated macular ganglion cell complex (GCC) thickness prediction from red-free fundus photographs by a hybrid deep learning model.

OCT FOR RETINAL NERVE FIBRE LAYER AND GANGLION CELL COMPLEX

Structural analysis of retinal nerve fiber layer (RNFL) and GCC has become an invaluable tool in the arsenal of glaucoma diagnostics. The basic disc, RNFL and GCC parameters including disc area, NRR area, RNFL thickness, etc., measured by the OCT software, is by image segmentation, which is an artificial Intelligence method. But making sense of the results automatically becomes a game changer. Even systemic diseases such as Alzheimer's disease,[26,27] Parkinson's disease[28,29] and even mild cognitive impairment[30] can have OCT RNFL changes as noted in the cited articles.

Muhammad[31] and the team showed that their hybrid algorithm had 93.1% sensitivity in the OCT detection of glaucoma. Barella *et al.*,[32] Bizios *et al.*[33] and Larrosa *et al.*[34] also studied ML algorithms that used OCT RNFL for the detection of glaucoma. Christopher *et al.*[35] predicted glaucoma progression by OCT RNFL findings. Meanwhile, Asaoka *et al.*[36] used AI on OCT macula (GCC) to detect glaucoma.

Park *et al.*[37] developed a novel algorithm that combined OCT RNFL and OCT GCC to predict 24-2 VF with an error of only 4.70 dB. The accuracy of this prediction was not affected by factors such as age, visual acuity, spherical equivalence, axial length, and OCT signal strength.

ANTERIOR SEGMENT OCT

Fu *et al.*[38] demonstrated the use of AI to automatically segment various clinical structures at the angle and the estimation of the anterior chamber angle (ACA) of the eye. Niwas *et al.*[39] looked at the problem from another angle, and developed an automated method of classifying angle closure glaucoma (ACG) mechanisms into four types – exaggerated lens vault, pupil block, thick peripheral iris roll, and plateau iris.

INTRAOCULAR PRESSURE (IOP)

IOP is conventionally the only modifiable risk factor of glaucoma and it makes sense to use AI to predict progression of glaucoma from IOP measurements. Continuous IOP measurements by smart contact lens Sensimed Triggerfish (Sensimed AG, Lausanne, Switzerland) are AI-generated from corneal strain measurements. Data from 24 prospective studies of this device were used by Martin *et al.*[40] to identify parameters specific to glaucoma patients.

VISUAL FIELDS (VF)

The functional status of glaucoma damage is assessed by visual field perimetry, mostly by standard automated perimetry (SAP), the most commonly used of which is the Humphrey field analyzer (HFA). AI algorithms can help in quick and accurate interpretation of VF. The newer headset-based virtual reality perimeters,[41] such as PeriScreener, iVA, Elisar, C3FA, and VirtualEye, are ideal tools where these algorithms can be readily implemented.

Preperimetric glaucoma is defined as the earliest stage of glaucoma where visual field defects are not seen, but structural changes may be seen in OCT RNFL. Asaoka *et al.*[42] from the University of Tokyo demonstrated that Preperimetric glaucoma can be detected from normal appearing perimetry reports without using OCT by using a deep feed-forward neural network (FNN). Li *et al.*[43] demonstrated that their

algorithm had higher accuracy than human ophthalmologists for differentiating glaucomatous from non-glaucomatous visual fields while Andersson *et al.*[44] showed similar results with their algorithm. Goldbaum *et al.*[45] used unsupervised machine learning to extract meaningful patterns from SAP field tests. Thakur *et al.*[46] used convex representation using deep archetypal analysis of visual fields to detect preclinical signs of visual field loss. Lee *et al.*[47] developed an algorithm that could predict the mean deviation of SAP of HFA from optic disc photographs.

Bowd *et al.*[48] used a machine language classifier to separate frequency doubling technology (FDT) perimetry data into glaucomatous and non-glaucomatous. Brigatti *et al.*[49] trained a neural network to detect glaucomatous visual field from Octopus perimtery. Kucur *et al.*[50] trained a custom convolutional neural network (CNN) to differentiate between normal and early glaucomatous visual fields acquired using the Octopus 101 G1 program. Huang *et al.*[51] developed a deep learning algorithm to grade glaucoma VF measured by Octopus perimeters.

Goldbaum *et al.*[52] used the progression of patterns (POP) algorithm to identify VF progression better than guided progression analysis (GPA). Yousefi *et al.*[53] also demonstrated an ML algorithm to detect glaucoma progression that performs better than global, region-wise, and point-wise indices, detecting even slowly progressing eyes.

FORECASTING FUTURE VF

Thakur *et al.*[54] developed a deep learning system capable of predicting future glaucoma from fundus photographs 4 to 7 years before it is apparent to human ophthalmologists on the fundus photographs. Lee *et al.*[55] used a different approach where they used a DL algorithm that estimated RNFL thickness from fundus photographs to predict the progression of glaucoma suspects to true glaucoma.

Park *et al.*[56] built a VF predicting Recurrent Neural Network (RNN) algorithm which was fed 5 consecutive visual fields and predicted the next visual field test for that patient. Even more interesting is the work by Wen *et al.*[57] who were able to predict the future HFA 24-2 visual fields of specific patients for up to 5.5 years using a single HFA report. They did this by training the algorithm on 32,443 VF reports of 4,875 patients from a 20-year period, which included around 1.7 million perimetry points. Yet another study by Kazemian *et al.*[58] generated personalized forecasts of open angle glaucoma visual field progression at different IOP levels. This would help to set personalized target IOPs considering the clinic-patho-physio-psycho-socio economic nature of the disease.

However, when Eslami *et al.*[59] evaluated two novel visual field forecasting tools, they noted that even though the overall mean absolute error was low, both models underpredicted the worsening of VF loss. CNN data set included 54,373 samples from 7,472 patients, and the RNN data set included 24,430 samples from 1,809 patients. Sahil Thakur *et al.*[60] reviewed several publications on AI models that forecasted glaucoma progression.

COMBINED APPROACHES

Glaucoma cannot be adequately assessed by a single investigative modality, hence an approach that combines various glaucoma investigations is more trustworthy than a diagnosis from a single test. Oh *et al.*[61] used an artificial neural network (ANN) to screen for glaucoma using age, sex, menopause, hypertension, IOP, spherical equivalent, vertical cup-disc ratio, superotemporal RNFL defect, and inferotemporal RNFL defect. They suggest that subjective and time-consuming visual field tests can be avoided for such screening.

CONCLUSION

The rise of all these technologies shows us that it is indeed the time for teleophthalmology, virtual glaucoma clinics, and uberization of eye care.[62] This would allow ophthalmologists to use these tech tools to efficiently screen and diagnose patients quickly and with minimum necessary investigations. Treatment can be monitored closely by algorithms that detect small but true progression, and future visual fields can be predicted at various target IOPs, allowing customization of treatment to individual patients. But we should not trust AI[63] reports blindly, and must ultimately remember that it is the human ophthalmologist who should have the final say, and human supervision[64] is indeed necessary for artificial intelligence.

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Conflicts of interest

There are no conflicts of interest.

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Straatsma syndrome: An unusual cause of refractory amblyopia

DESCRIPTION

A six-year-old girl was brought to the pediatric ophthalmology clinic by her mother in view of deviation of her left eye (LE) since five months of age. There was no relevant family history or systemic illness contributing to her squint. She underwent a complete ocular examination. Hirschberg test showed 30-degree exotropia LE. The cover uncover test showed exotropia LE with full extraocular motility in both eyes. Left eye suppression was manifested on sensory examination. Her best-corrected visual acuity was 6/6 in the right eye (RE) and Counting Fingers three meters LE using Snellen's visual acuity chart. Under cycloplegic retinoscopy, RE showed normal refraction (+1.25 diopter sphere), however, there was a refractive error of −10 diopter spheres with a −2.5 diopter cylinder at 180° LE. Anterior segment examination under the slit lamp was within normal limits in both eyes. Dilated fundus examination showed the presence of myelinated nerve fibers (MRNF) LE along the superior, inferotemporal, and temporal arcades (superior > inferior); with a dull foveal reflex. The right eye fundus was normal [Figure 1]. Axial length was noted to be 21.95 mm RE and 26.24 mm LE with Lenstar LS 900 biometer (Haag-Streit Diagnostics, Germany); confirming axial myopia LE. Spectral Domain Optical coherence tomography (SD-OCT) depicted the thickening of the peripapillary retinal nerve fiber layer (RNFL) in the superior and temporal quadrants with thinning of the peripapillary retinal nerve fiber layer inferotemporally in the left eye [Figure 2]. OCT Macula revealed thickening except at the fovea [Figure 3]. Ultra-wide field OCT LE showed extensive thickening of RNFL along the superotemporal, inferotemporal vascular arcades and temporally in the region of the macula with sparing of fovea [Figure 4 a-c]; corresponding to the area of MRNF. Ganglion cell layer (GCL) thickness evaluation was unreliable due to difficulties in segmentation. She has prescribed optical correction in the form of spectacles for the left eye and occlusion therapy for the right eye. Follow-up at six months and one year did not show any improvement in visual acuity LE despite good compliance with glasses and occlusion therapy.

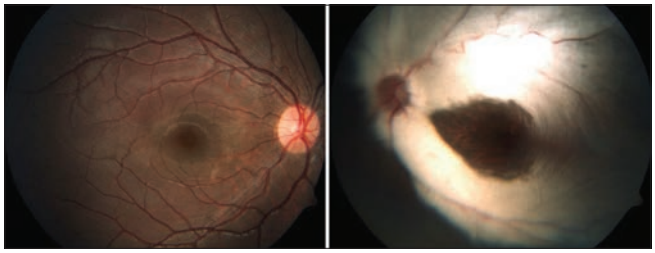


Figure 1: Color fundus picture showing normal fundus RE and myelinated nerve fibers (MRNF) LE along the superior, inferotemporal and temporal arcades (superior > inferior); with a dull foveal reflex

DISCUSSION

Myelinated retinal nerve fibers (MRNF), are gray-white well demarcated lesions with frayed borders on the retina. These fibers have a myelin sheath, unlike normal retinal nerve fibers. Bradley R Straatsma *et al*.[1] described an unusual presentation of a triad of unilateral MRNF, amblyopia, and high myopia as Straatsma syndrome (STAS).

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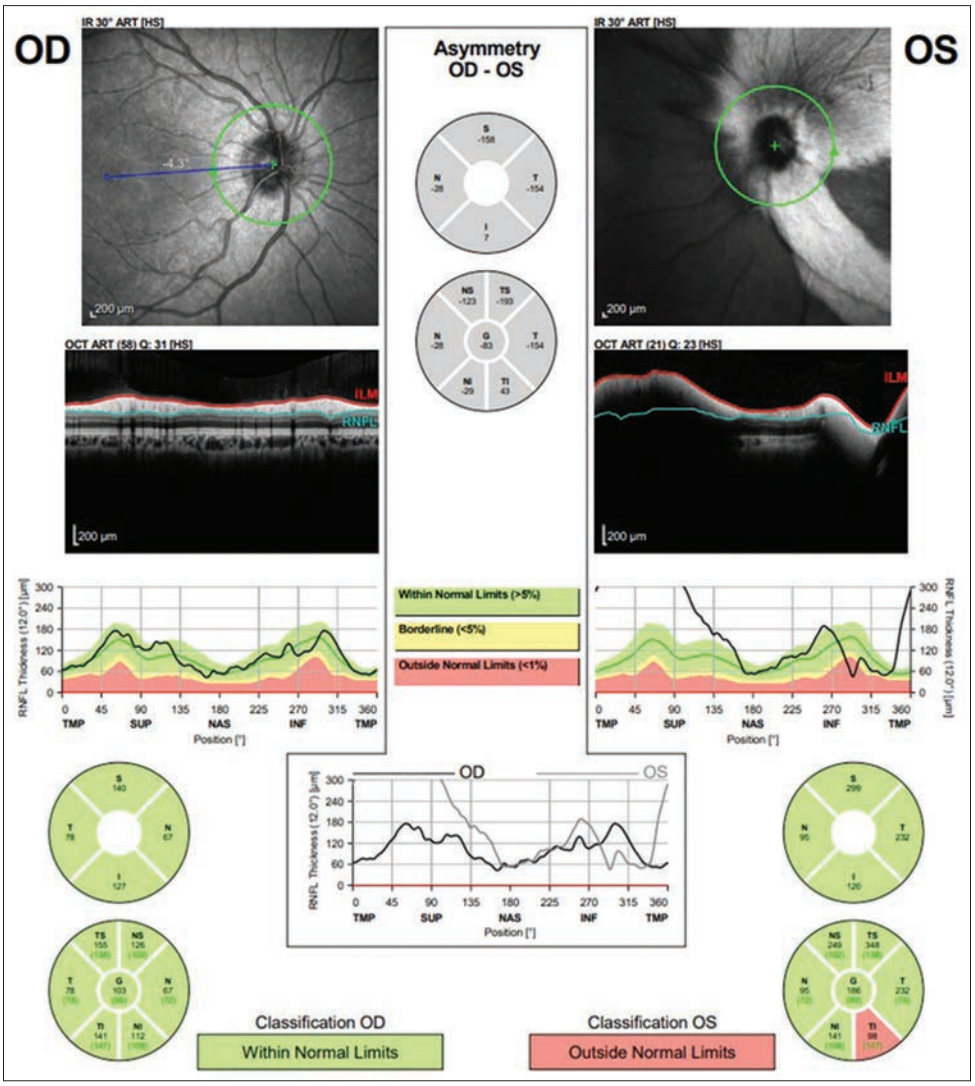


Figure 2: SD-OCT of the peripapillary retinal nerve fiber layer (RNFL) showing normal values RE and thickening in the superior and temporal quadrants with thinning infero-temporally LE

Here, we report a case of STAS in a young girl exhibiting unilateral high myopia, amblyopia, and MRNF associated with strabismus.

Being a benign and incidental finding, the presence of MRNF is seen in about 0.57% -1% of the population.[2] Though the pathogenesis is not fully known, possible theories explained so far include disruption of lamina cribrosa which acts as a barrier for myelination, and migration of heterotopic cells into the retina during in-utero development.[3] Three forms of MRNF were described by Ellis *et al*.[4] include: Type 1 where one temporal arcade of the retinal nerve fiber layer is affected, Type 2 where both temporal arcades are affected, and Type 3 where fibers are non-contiguous with the disc. As per this classification, our patient had Type 2 MRNF. Other associations include strabismus, heterochromia iridium, nystagmus, retinal telangiectasia, vitreoretinal degenerations, familiar myelinated retinal fibers, coloboma, keratoconus, neurofibromatosis, and Down syndrome. Sometimes, hyperopia may be associated and is known as Reverse Straatsma syndrome.[5] High myopia and strabismus in the form of exotropia were seen in our patient.

Straatsma[2] describes that myelin fibers interfere with ocular development preventing the transmission of retinal impulses to the lateral geniculate nucleus. This in turn would cause visual deprivation and axial elongation of the eye. Amblyopia can be due to structural defects by myelin fibers, refractive error, or even strabismus; as was seen in our patient also. SD-OCT was able to demonstrate the extensive thickening of RNFL along the superior and inferior vascular arcades and temporally in the region of the macula except at the fovea; confirming the structural change in the area of MRNF. Although prognosis is guarded in these patients, therapeutic

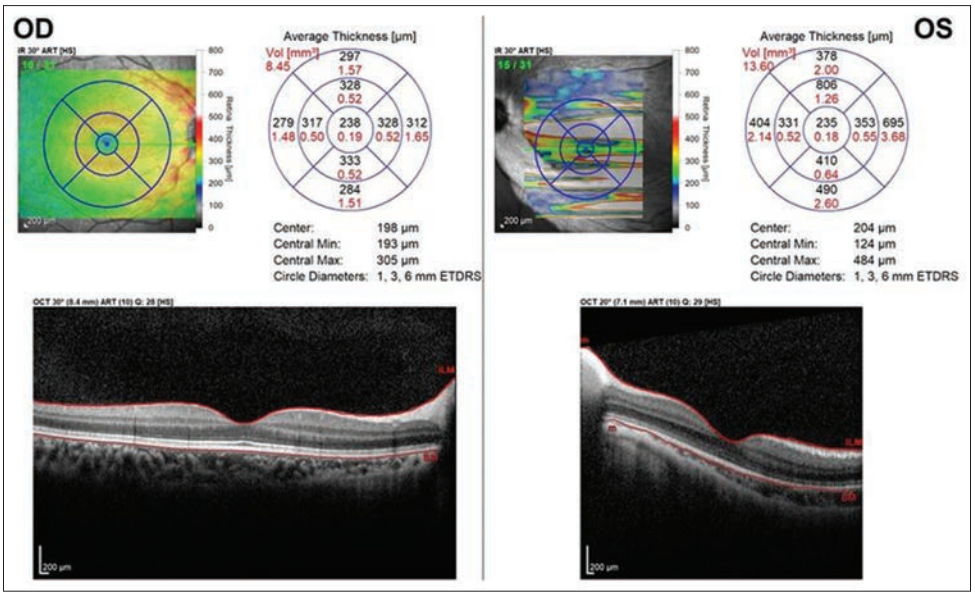


Figure 3: SD-OCT Macula revealed normal values RE and thickened retinal layers; except at the fovea LE

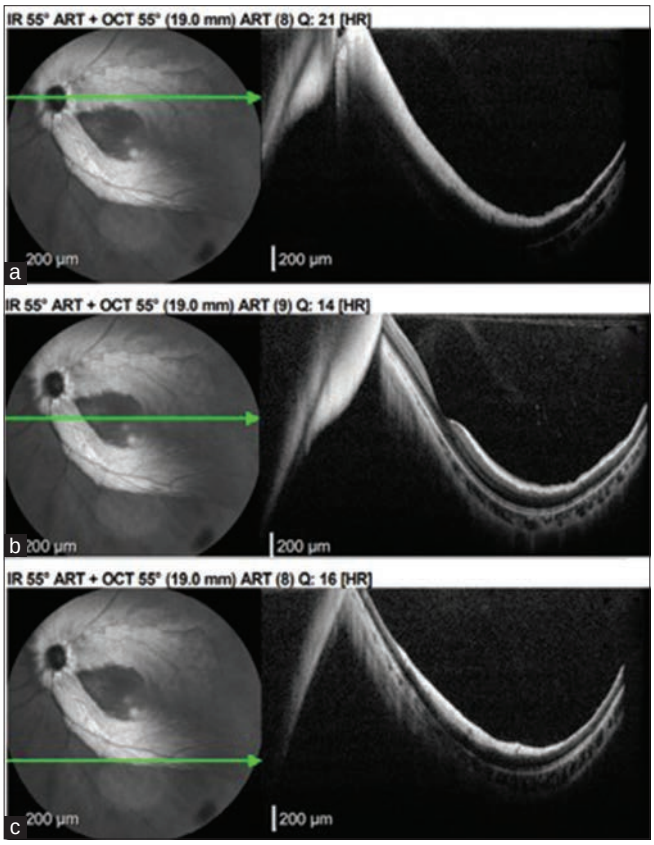


Figure 4: (a-c): Ultra-wide field OCT LE showed extensive thickening of RNFL along the superotemporal, inferotemporal vascular arcades and temporally in the region of macula with sparing of fovea

options include optical correction for myopia and occlusion therapy for amblyopia. In our patient, late presentation, the presence of unilateral high myopia, extensive myelinated fibers, and exotropia possibly contributed to the dense amblyopia and poor visual improvement.

CLINICAL SIGNIFICANCE

Though myelinated fibers are considered innocuous, it is important for every ophthalmologist to understand its important variant- Straatsma syndrome; a triad of

unilateral myelinated retinal nerve fibers, high myopia, and amblyopia, the presence of which comes with a guarded visual prognosis. Very often, it goes undiagnosed due to unawareness of its features. An early diagnosis, adequate optical correction, a robust trial of amblyopia therapy, and empathetic counseling regarding guarded visual prognosis would help in the management of this unusual clinical condition.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Title, abstract, keywords, and authorship criteria

ABSTRACT

In the domain of medical research, the importance of developing precise and informative elements such as the title, abstract, keywords, and authorship criteria cannot be overstated. This article provides salient points on drafting these essential components for effective communication, dissemination, and ethical behavior in the medical research field.

Keywords: Abstract, authorship criteria, title

INTRODUCTION

An effective title and abstract for a research paper are crucial as they are the first element that readers encounter. An effective abstract provides a brief overview of the research, helping readers quickly understand the purpose, methodology, results, and significance of the works. The keywords give the essence of an article. The keywords help the readers to find an article quickly and accurately. Any person who has made a significant contribution to a journal article is an author.

SALIENT POINTS

a. Title

- Title should be able to stand alone as an explanation of the study. Most of the electronic search engines, databases, and journal websites will use the words in the title for retrieval of an article. The title should try to incorporate the patients or subjects of the study, interventions or exposures, comparisons, and outcomes. A good title typically contains 15–20 words.
- There are three types of title: **Declarative titles**—state the main findings or conclusions, **Descriptive titles**—describe the subject of the article but do not reveal the main conclusions. **Interrogative titles**—introduce the subject in the form of a question.

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b. Abstract

- The title and abstracts are the only sections of the research paper that are often freely available to the readers on journal websites, search engines, and in many abstracting agencies/databases. The abstract is an independent and standalone (that is well understood without reading the full paper) section of the manuscript and is used by the editor to decide the fate of the article and to choose appropriate reviewers.
- The abstracts can be structured or unstructured. Some journals stick to a four-point structured format for the structure of the abstracts, and the subheadings would include the following: introduction or background, method, results, and conclusion.
- It is important to stick to the instructions to authors provided by the journal for which the abstract and the paper are being written. Most journals allow 200–300 words for formulating the abstract and it is wise to restrict oneself to this word limit.
- It is recommended to draft the abstract in the end to maintain accuracy and conformity with the main text of the paper.

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c. Keywords

- The title and abstract should be composed using keywords (key terms/important words) drawn from all sections of the main text. These terms are specifically chosen by the authors to emphasize the primary subject and discoveries of the article.
- Their purpose is to enhance the visibility of the article in search engines and databases. Medical Subject Headings (MeSH) terminology comprises a standardized collection of terms authorized by the National Library of Medicine for indexing articles in PubMed and similar databases.[1] Authors are advised to employ keywords from the MeSH vocabulary to optimize discoverability.

d. Authorship criteria

The criteria for authorship in medical journals have been clearly defined by the International Committee of Medical Journal Editors.[2] These criteria include the following:

- Making substantial contributions to the conception or design of the work, as well as to the acquisition, analysis, or interpretation of data for the work.
- Authors must be involved in drafting the work or critically revising it for important intellectual content and must give their final approval for the version to be published.
- Authors must agree to be accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMMON MISTAKES/PITFALLS

1. Failure to create a title that is both descriptive, direct, and accurate is a common error.
2. Premature drafting of the title and abstract before the completion of the full manuscript is another common mistake.
3. A frequent mistake involves not following the specific formatting and instructions provided by the target journal for the title and abstract

TAKE HOME MESSAGES

A concise title, an informative abstract with keywords, and ethical authorship standards are imperative to enhance the dissemination and influence of one's research findings. Adhering to these straightforward principles will guarantee that your scholarly contributions receive the appropriate recognition they deserve.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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1. MeSH terms. Available from: https://www.ncbi.nlm.nih.gov/mesh/.
2. International Committee of Medical Journal Editors (ICMJE). Available from: https://www.icmje.org/recommendations/.

Curated article summaries

1. SHORT-TERM DETECTION OF FAST PROGRESSORS IN GLAUCOMA: THE FAST PROGRESSION ASSESSMENT THROUGH CLUSTERED EVALUATION (FAST-PACE) STUDY

Medeiros FA, Malek DA, Tseng H, Swaminathan SS, Boland MV, Friedman DS, Jammal AA. Short-term Detection of Fast Progressors in Glaucoma: The Fast Progression Assessment through Clustered Evaluation (Fast-PACE) Study. Ophthalmology. 2024 Jun; 131(6):645-657. doi: 10.1016/j.ophtha.2023.12.031. Epub 2023 Dec 29. PMID: 38160883.

SUMMARY

Generally, in most patients with glaucoma, it takes years to display the deterioration (slow progressors), whereas in some it may progress rapidly (fast progressors). Fast progressors may show worsening despite a well-controlled intraocular pressure (IOP) and may require neuroprotective therapies to prevent blindness. The clinical trials to assess progression outcomes require large sample sizes or long follow-up periods to identify rates of disease worsening and hence many other strategies have been proposed one of which is the clustering tests at both ends of the observation period.

Fast-Progression Assessment through Clustered Evaluation (Fast-PACE) study was an observational cohort study by Bascom Palmer Eye Institute and Duke Eye Center in which 65 diagnosed cases (125 eyes) of primary open-angle glaucoma with glaucomatous-appearing optic discs in both eyes and at least one eye showing evidence of corresponding repeatable abnormal standard automated perimetry (SAP) test results were enrolled. The main objective was to assess the feasibility and efficacy of detecting fast progressors in a short time by intensive clustering. Subjects underwent two clusters of testing (five visits each at weekly intervals) 6 months apart. At each visit, IOP, 24-2 and 10-2 SAP, and optical coherence tomography (OCT) were taken. The participants were also seen in an extended follow-up period postclustering.

Analyses of SAP 24-2 and 10-2 mean deviation and spectral domain OCT global peripapillary retinal nerve fiber layer (RNFL) thickness showed that approximately one in five eyes progressed based on 24-2 or 10-2 testing over 6 months and a significant proportion of eyes also progressed by RNFL measured. The clustering method detected fast progressors with a high sensitivity, which is an important result because identifying fast-progressing eyes at the outset of treatment could lead to more rapid escalation of treatment, which should reduce glaucoma-related disability. The absence of progression during the cluster period strongly indicates a low probability of an eye being a fast progressor during the extended follow-up.

WHY THIS ARTICLE?

Global metrics provide a simple measure of the rate of change and have been widely demonstrated to predict disability in glaucoma. The intensive clustered testing methodology used in this study not only offers promising implications for clinical trials investigating interventions including neuroprotective therapies to slow down glaucoma progression but also be of value for short-term assessment of high-risk subjects.

2. CORRELATION OF CLINICAL AND RADIOLOGICAL SCORES FOR EVALUATION OF ACTIVITY IN PATIENTS HAVING THYROID-ASSOCIATED ORBITOPATHY: A PROSPECTIVE OBSERVATIONAL STUDY

Singh, Manpreet; Rana, Neeti; Ahuja, Chirag1; Gupta, Pankaj; Zadeng, Zoramthara. Correlation of clinical and radiological scores for evaluation of activity in patients having thyroid-associated orbitopathy: A prospective observational study. Indian Journal of Ophthalmology 72(6):p 844-848, June 2024. | DOI: 10.4103/IJO.IJO_1702_23

SUMMARY

The characteristic feature of thyroid-associated orbitopathy (TAO) is the inflammatory enlargement of extraocular muscles (EOMs) and orbital fat. The two stages of TAO, the active and inactive, are diagnosed by clinical evaluation and radiological features. There are various scoring systems used to grade the activity of TAO of which vision–inflammation–strabismus–appearance (VISA classification) assesses the disease's activity and severity. Magnetic resonance imaging (MRI) provides the details of the orbital soft tissues, mainly EOM and fat, and diffusion-weighted imaging (DWI) is used to detect microstructural changes in various tissues. DW-MRI can objectively quantify the activity of the disease in TAO.

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This was a prospective observational study conducted in 33 patients with treatment-naïve TAO by the Post Graduate Institute of Medical Education and Research, Chandigarh, to find a correlation between VISA classification (clinical) and apparent diffusion coefficient (ADC) values in DW-MRI (radiological). All patients underwent a detailed history recording and ophthalmic examination according to the VISA classification system and were categorized into mild, moderate, and severe TAO. Any patient with defective color vision with visual field changes (unilateral or bilateral) was defined as dysthyroid optic neuropathy (DON). The orbital MRI was performed using a 3.0 T system with T2-weighted (T2W) fat-saturated axial, T2W coronal, and T1W axial and coronal sequences. The thickness of EOMs, proptosis, and EOMs' ADC values were noted. Schirmer's test, eyelid retraction, Hertel's exophthalmometry, and perimetry were performed.

On analyzing the data, a positive correlation between the patients' ADC values and EOM thickness was obtained. The correlation was strongest between medial rectus thickness and ADC, followed by inferior rectus. This study also found that ADC values of EOMs correlate well with the inflammation score of VISA classification and can predict the activity of TAO. ADC value of the inferior rectus can predict the activity of disease with 68% sensitivity and MR ADC with 87% sensitivity.

WHY THIS ARTICLE?

TAO is one of the most common autoimmune diseases of the orbit. Clinically, the challenge is to recognize the active, inflammatory phase of the orbital disease. In fact, early diagnosis and rapid introduction of anti-inflammatory treatment, mainly steroids, improve the final outcome and reduce the functional and disfiguring sequelae of the disease. The activity of the disease is the determining factor in planning the treatment for the best possible outcomes in TAO patients. The ADC values on DW-MRI provide objective values of the ongoing inflammation in EOM providing a baseline to be monitored after completing the pulse dose regimen of intravenous steroids or other drugs and the need for additional doses of steroids during the course of the treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Deciphering the uveitis quagmire

ABSTRACT

Differential diagnosis of uveitis, the role of immunosuppressives and biologics in the management.

Keywords: Anterior, immune privilege, intermediate, posterior, uveitis

The success in the management of uveitis is determined by its early diagnosis and adequate treatment, the failure of which will cause irreparable blindness. Diagnosis is challenging, even more its management in the next paragraph line 16 [Figures 1 and 2].

The Ninja Warrior of Uveitis: Immunosuppressives

Uveitis is an inflammatory condition that begins in the uvea but can also affect nearby eye components. Although corticosteroids are the most commonly used treatment, other immunosuppressive medications are frequently used as well which involve inhibitors or antibodies against the inflammatory cytokines.

Eyes: the VIPs of immunity

The eyes have an "immune privilege" that enable them to preserve tissue integrity as well as a low degree of immunity that prevents unwanted and permanent consequences of any inflammatory response.[3]

The hemato-retinal barrier and the absence of lymphatic drainage are some anatomical mechanisms that contribute. Molecular mechanisms include the secretion of soluble immunosuppressive factors, such as β-TGF and Fas ligand (FasL), and the low expression of MHC class II molecules in APCs.

These also suppress the proliferative ability of T-cells and deactivate the immune response of Müller cells and pigment epithelium cells that are capable of secreting anti-inflammatory cytokines. T regulatory cells (Tregs) maintain peripheral tolerance and prevent pathogen-induced immunopathology and autoimmune disorders.[4]

The presence of alloantigen in the anterior chamber results in an immunological tolerance known as anterior chamber-associated immune deviation (ACAID).

Breakdown of this ideal immunological equilibrium in the face of either endogenous/foreign aggression will cause a subsequent rise in proinflammatory cytokines (IL-2, IL-12, TNF-α, INF-γ, etc.) in contrast to anti-inflammatory ones (IL-4, IL-10, INF-α, etc.) leading to uveitis.

Figure 3 is the cascade:

1. Cyclosporine – The Immune Maestro Taming T lymphocytes

Cyclosporine binds to T-lymphocyte cyclophilin to inhibit calcineurin, and this complex initiates the downstream cascades required for the transcription of IL-2, CD40 ligand, and FasL.

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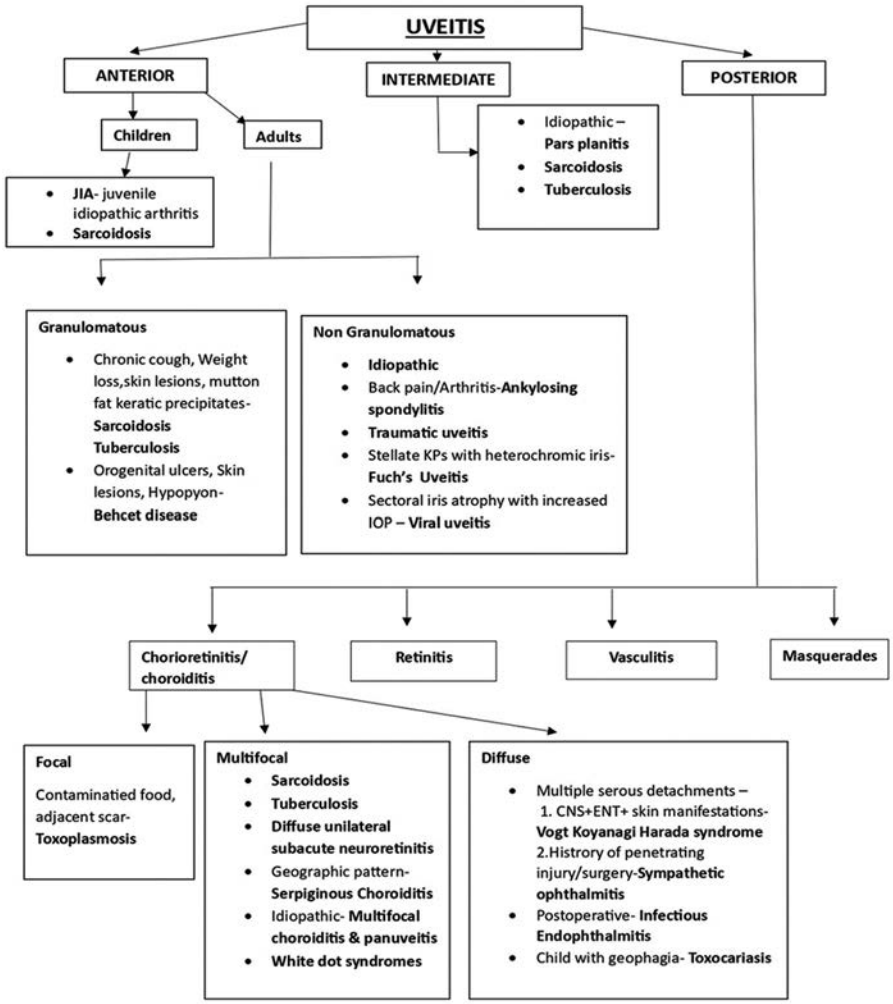


Figure 1: Meshing through the differentials[1,2]

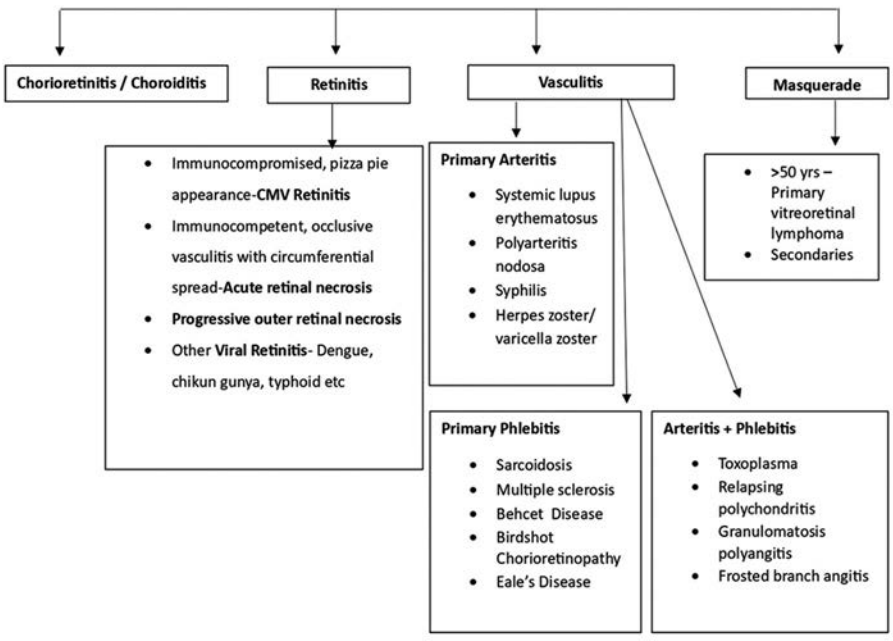


Figure 2: Meshing through the clinical features[1,2]

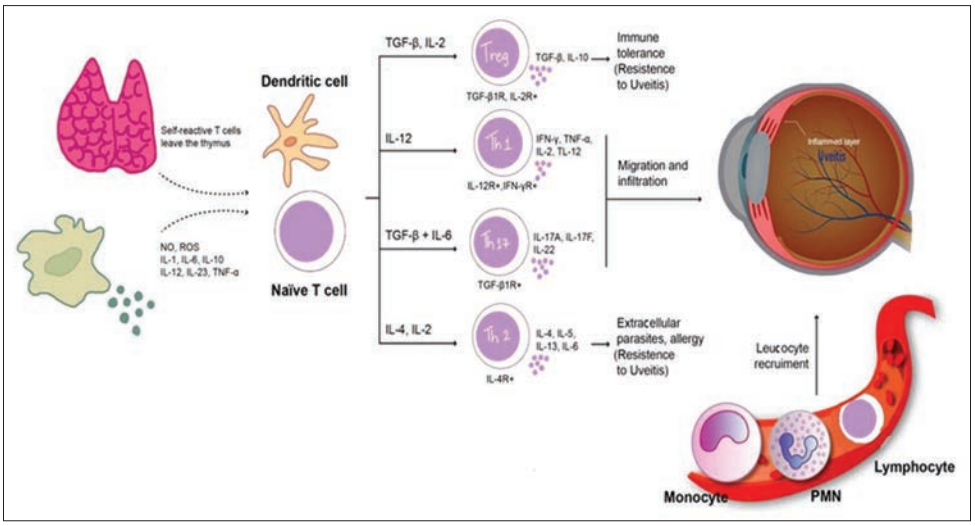


Figure 3: The uveitic cascade

BIOLOGIC	MECHANISM OF ACTION	DOSE
Infliximab	Anti TNF alpha	IV; 3-5mg/kg at weeks 0,2,6 subsequently every 4-8 weeks depending on disease control
Adalimumab	Anti TNF alpha	SC; 40mg SC every 2 weeks
Golimumab	Anti TNF alpha	SC; 50mg every 4 weeks OR IV; 2mg/kg every 4 week twice then every 8 week
Gevokizumab	Anti IL- 1 beta	Single infusion of 0.3mg/kg (along with Oral Prednisolone
Tocilizumab	Anti IL-6 receptor	IV; 4mg/kg or 8mg/kg every 4 weeks OR SC; 162mg/week
Daclizumab	Anti CD25 (IL 2 receptor)	IV; 1mg/kg every 2-4 weeks OR 2mg/kg on day 1, repeating on day 14 OR SC; 2mg/kg every 4 weeks
Alemtuzumab	Anti CD 52	IV; 12mg/day for 5 days
Rituximab	Anti CD 20	IV; 1000mg/day on day 1 and 15, repeated after 6 months OR 375mg/m^2 body surface area/week for 8 weeks and then monthly for 4 months
Interferons	Non specific	*IFN alpha 2a*: SC/IM; 3-6 MIU daily – 3 times/day
		IFN alpha 2b: SC; 3-4.5MIU / day for 2 weeks tapering over 3 weeks
		IFN beta: SC; 44 micro grams 3 times/ week

Figure 4: Biologics and its specific targets[6]

The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, a multicenter study in the United States, found that only 33.4% of patients at 6 months received comprehensive and long-lasting relief from inflammation, indicating that the benefits of cyclosporine were minimal.[5]

2. Metabolic Mediators – Antimetabolites

Methotrexate (MTX) functions by competitively binding to the enzyme dihydrofolate reductase and preventing the formation of purines and pyrimidines, which in turn inhibits DNA synthesis and prevents cell division. It may also cause T-cell apoptosis, and decrease cytokine generation.

In the SITE trial, 66% of the 384 individuals examined in a single year had all their ocular inflammation completely

MEDICATION	DOSE		COMMON SIDE EFFECTS
Antimetabolites (MTX, MMF, Azathioprine)	Azathioprine	Orally: 2-3mg/kg/day then titrated according to response	Gastrointestinal upset Bone marrow suppression
	Methotrexate	Orally/IM 2.5-10mg/week and titrated to effect	
	MMF	500mg BD and then increased to 1g BD after 2 weeks	
T cell inhibitors (Cyclosporine, Tacrolimus)	Cyclosporine	Orally: 2.5-5mg/kg BD	Renal toxicity Hypertension Neurological symptoms GI symptoms (Tacrolimus) Hyperglycaemia (Tacrolimus)
	Tacrolimus	Orally: 0.03-0.08mg/kg/day	
Alkylating agents (Cyclophosphamide, Chlorambucil)	Cyclophosphamide	Pulsed IV- infusions at 2 weekly intervals titrated to a leukocyte count of 3500-4500 cells/micro litre	Bone marrow suppression Cystitis, Hematuria (Cyclophosphamide)
	Chlorambucil	Orally: 0.1mg/kg/day with titration to response	
TNF inhibitors (Infliximab, Adalimumab)	Dose in previous table		Infusion/hypersensitivity reactions Autoantibody formation

Figure 5: Common immunosuppressives and their dose[7,8]

resolved with MTX, validating MTX to be more advantageous than cyclosporine, which yielded a 51.9% result in the same timeframe. However, 16% of patients stopped treatment due to the drug's side effects mainly hepatotoxicity and myelosuppression.[5]

Mycophenolate Mofetil was also assessed with a remission rate of 53%

3. Biologic Guardians – Revolutionizing Ophthalmic Immunosuppression

In recent times, new targeted therapies have been developed that interfere with the function of specific molecules that cause inflammation and tissue damage.

Figures 4 and 5 show the dose, mode of action, and side effects.

CONCLUSION

The use of biologics underlines the key roles of inflammatory cytokines, T-cells, and B-cells in the pathogenesis of inflammatory uveitis.[9] The antimetabolites and biologics offer the best balance between effectiveness and safety and pose excellent alternatives to treat high-risk uveitis syndromes unresponsive to corticosteroids alone while preventing corticosteroid-induced toxicity.

Test yourself (the answer will be given in the next issue)

Which of the following immunosuppressants is a selective T-cell costimulation modulator used in the treatment of noninfectious pediatric uveitis?

A) Methotrexate
B) Mycophenolate mofetil
C) Adalimumab
D) Abatacept

Answer to the previous issue MCQ: (C) is the false statement.

The correct statement is that ABCG2 is present in less than 10% of the limbal basal cells.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Double capsulorhexis technique for safe phacoemulsification in intumescent cataract

ABSTRACT

Intumescent white cataracts are a challenge for novice and experienced surgeons alike. Creating a continuous curvilinear capsulorhexis may pose a problem in these cataracts due to many factors like increased intra capsular pressure, absence of red reflex, poor visibility, fragile or calcified anterior capsule.[1] These cataracts tend to have a shallow anterior chamber and presence of fluid vacuoles or sectoral markings in subcapsular area which can be seen on slit lamp biomicroscopy.[2] Argentinian flag sign, which is a radial tear in anterior capsule, can occur while creating capsulorhexis, due to raised intracapsular pressure.[3] Radial tears extending to the equator, makes phacoemulsification unsafe, since it may lead to further complications such as extension of the tear to posterior capsule, nucleus drop in vitreous cavity and difficulty with IOL placement. This video demonstrates the steps of 2 staged capsulorhexis, to prevent radial extension while operating a type 1 (liquified cortex) intumescent cataract and type 2 (no liquified cortex, only tense fibres) intumescent cataract.[4]

Keywords: Capsulorhexis, hypermature cataract, intumescent cataract

Link of video:

https://drive.google.com/file/d/1Vq7uLgcFgL1-EcMH0W-f7VrDlL3QNJ1P/view?usp=drivesdk.

FOCUS POINTS

- Stain the anterior capsule with trypan blue 0.06% for better visibility
- Use cohesive (sodium hyluronate3%) or viscoadaptive (sodium hyluronate 2.3%) viscoelastic device (OVD) to flatten the anterior capsule
- Use small side ports to avoid leakage of OVD
- A small < 3mm curvilinear rhexis is made using 26 gauge needle cystitome or micro-rhexis forcep
- A 27 gauge hydro cannula is used to aspirate the liquified cortex in type 1 intumescent cataract and decompress the mid peripheral tense cortical fibres in type 2 intumescent cataract
- Micro-rhexis scissors and micro-rhexis forceps are used to fashion the second larger capsulorhexis
- Mid peripheral zone having tense cortical fibres cause the rhexis flap to extend outwards, it is important to observe the direction of advancing flap and pull it inwards at appropriate stages.

CONCLUSIONS

Correct identification of intumescent cataracts preoperatively and following the steps correctly to decompress the intralenticular pressure intraoperatively can help prevent capsulorhexis-related complications in intumescent cataracts.

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Comment: Knowledge attitude and practice regarding "over-the-counter" prescription of topical eye steroid among the pharmacists/medical shopkeepers

Dear Editor,

We have read with keen interest the recently published study titled "knowledge attitude and practice regarding "over-the-counter" prescription of topical eye steroid among the pharmacists/medical shopkeepers" by Singh, *et al*.[1] We wish to express our commendation to the authors for their invaluable contribution to the field of ophthalmology, particularly for shedding light on a significant aspect of ophthalmic care concerning the dispensation of topical eye steroids over the counter (OTC) by pharmacists and medical shopkeepers.

Although the study provides valuable insights into the knowledge, attitude, and practice of pharmacists regarding OTC prescription of topical eye steroids. We would like to provide some feedback and recommendations that we believe would enhance the comprehensiveness and impact of this research.

The study conducted among only 60 pharmacists/shopkeepers in a specific district of Madhya Pradesh, India, raises concerns about its representativeness for the broader population of pharmacists/medical shopkeepers in the region or the country. In addition, the single geographic location of the study limits the generalizability of its findings.[2]

The reliance on self-reported information through questionnaires introduces the possibility of social desirability bias, wherein participants may provide responses they perceive as socially acceptable rather than reflecting their actual practices. This bias could lead to inaccurate estimations of behaviors or attitudes. Although the study provides valuable insights into the challenges and practices prevalent among pharmacists in a specific geographic region, it is essential to recognize the limitations inherent in the study design, such as the small sample size and potential biases associated with self-reporting.[3]

Furthermore, although the study mentions obtaining permission from an ethical committee and verbal informed consent from participants, it lacks details on ethical considerations such as confidentiality, anonymity, and voluntary participation, which are crucial in ensuring ethical conduct in research involving human participants.[4]

We commend for their commitment to advancing knowledge in this field. Their research provides valuable insights into the practices and challenges associated with the over-the-counter prescription of topical eye steroids by pharmacists. We encourage them to take into account these suggestions for their future research endeavors.

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Conflicts of interest

There are no conflicts of interest.

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"Management of ocular surface irregularity with scleral contact lenses: Experience from a tertiary eye care center" Author's reply to letter to editor

The authors thank Dr. Chaurasia[1] for the comments on our study. Our manuscript was "Management of ocular surface irregularity with scleral contact lenses: Experience from a tertiary eye care center."[1] This retrospective case series focused on selecting the indications of scleral contact lenses and studying their efficiency in treating severe corneal ectasia, highly irregular astigmatism, and ocular surface diseases, which are otherwise difficult to manage.

Our study is limited to those corneal pathologies where a spectacle correction or a gas-permeable lens correction was not possible. We included diverse corneal pathologies like irregular corneal scars like post penetrating injury, post chemical injury sequelae, severe corneal ectasia like moderate to severe Keratoconus, severe dry eye, Stevens-Johnson syndrome (SJS) sequelae, and xeroderma pigmentosa, and a sample size of 69 eyes is not a small sample size considering the cases selected as end-stage corneal pathologies.

The subject was already mentioned in our study about the wide range of age of the patients designated and also about the aid that the pediatric age group patients and the elderly patients need for lens insertion and removal.

The follow-up for a period of one year is adequate when the aim of the study is considered. The long-term effects of the lenses and complications are beyond the scope of this study and can be taken up in a follow-up study.

I, Jabbar A, sincerely thank the reviewers and the editorial team.

Faithfully,

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Conflicts of interest

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