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Cover Story:

Description:
This is the external photography image of the right eye of a 24 year old lady who came for routine ophthalmic examination. There are multiple iris strands along the pupil, inserted in the collarette, resembling a flower. Persistent pupillary membrane is a common congenital ocular anomaly and is a remnant of anterior tunica vasculosa lentis. Although the patient had a similar picture bilaterally, her vision was 6/9 in both the eyes, due to stenopeic effect.

Contributed by:
Dr. Hridya Mohan, Medical Officer, Cataract Services, Aravind Eye Hospital, Coimbatore

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Kerala Journal of Ophthalmology

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Connect, collaborate, contribute, and create

"No one is big enough to be independent of others."

-Will Mayo

As this Editorial team reaches the end of its 2 year tenure, I wish to thank each and every member of the team for the excellent teamwork and cooperation I received during this time. Selecting articles, reviewing, writing up sections, proofreading, and encouraging others to contribute, were all done in a timely and effective manner. Hopefully, we have together been able to raise the standards of our Journal. The encouragement and effective suggestions I received from my senior colleagues, timely reviews by expert reviewers from KSOS and outside, played a very important role in keeping the momentum going.

In my final editorial, I would like to highlight this extremely important concept of Teamwork and Collaboration. The concept of Networking for individual professional upliftment is gaining popularity. However, if we can cooperate with each other for the benefit of Ophthalmology as a whole, and patient treatment patterns, in particular, we reach nearer to our shared goal of reducing visual disability.

EVERYBODY WINS

The World Health Organization (WHO) recognizes that collaborative practice strengthens health systems and improves health outcomes, and is an innovative strategy that will play an important role in mitigating the global health workforce crisis. The Framework for Action on Interprofessional Education and Collaborative Practice is the product of the WHO Study Group on this practice.[1]

Collaboration is evident when health-care professionals communicate with each other, assume complementary roles to cooperatively work together, and share responsibility for problem-solving and decision-making. Specific collaborative activities include sharing of information, discussion of complicated cases, and referrals to colleagues. The developing concept of Group Practice and its advantages has been highlighted by the President, *KSOS*, in the following pages of this journal issue.

COLLABORATIONS IN OPHTHALMOLOGY

Being able to take care of the sight of a patient is both a responsibility and a privilege. Because this is our ultimate goal: to eliminate blindness and visual impairement. Many useful examples of cooperation have been seen in Ophthalmology.

Research

Collaboration is vital in driving forward research and innovation seeking to develop solutions to refine the diagnosis, management, and treatment of patients with eye diseases. There is a well-identified need for patient-oriented clinical research and this can only be achieved by creating active collaboration between academic centers with competence for clinical research, with support by an infrastructure that provides appropriate management of clinical trials at a realistic cost. In Ophthalmology, the example was set by the Diabetic Retinopathy Clinical Research (DRCR. net) Retina Network in the USA, formed in 2002 through a National Eye Institute and National Institute of Diabetes and Digestive and Kidney Diseases-sponsored cooperative agreement. The objective was to develop a collaborative network to facilitate multicenter clinical research on Diabetic Retinopathy and Diabetic Macular Edema, and has now been expanded to include research on other retinal diseases. It used the combined strengths of academic and community retina sites in the infrastructure as well as created opportunities for industry collaboration while maintaining rigorous academic independence from pharmaceutical interests.[2] Since 2002, the DRCR. net has initiated and completed numerous multicenter studies in DR with over 160 participating sites and 500 physicians throughout the United States and Canada.

Multicenter Data Retrieval

Data from various sources can be integrated into a common registry and provide important information. Useful applications can be derived too from these. Data derived from the Sight Outcomes Research Collaborative Ophthalmology Data Repository, which captures electronic health record data of all patients receiving any eye care at academic medical centers, was used for developing an algorithm useful in triaging patients in the COVID pandemic based on glaucoma severity and progression risk by identifying patients whose

appointments could safely get postponed and facilitated prioritization of appointments for rescheduling.[3]

Clinical Practice Guidelines

We are beginning to work together to develop consensus statements about eye care and train ourselves on how to use best practice guidelines. An international, expert-led consensus initiative was set up by the Collaborative Ocular Tuberculosis Study group to develop systematic, evidence, and experience-based recommendations for the treatment of ocular TB using a modified Delphi technique process.[4]

Sharing Knowledge And Expertise

Improving education and training to raise standards in Ophthalmology worldwide[5,6] is being followed by many important organizations, and is best exemplified by the online academic resource, EyeWiki, which is a collaboration between the American Academy of Ophthalmology and multiple societies.[7]

Networking for Professional Career Advancement

There is a critical need to help ophthalmologists maintain their competency and learn new skills, forging valuable relationships with peers. Organized mentorship programs can play a key role in fostering the development of careers in ophthalmology.[8] Stronger personal relationships can nurture innovative strategies with colleagues, engage new energy, and maintain momentum when obstacles seem overwhelming.

Public Education

Public–private partnerships can improve population health by advancing public health strategies and policies, improving public health education and advocacy, fostering trust and collaboration among sectors and stakeholders, and improving access to health care.[9]

Newer Technologies

A universal artificial intelligence (AI) platform developed for collaborative management of cataracts involving multilevel clinical scenarios explored an AI-based medical referral pattern to improve collaborative efficiency and resource coverage. It showed robust diagnostic performance and effective service for cataracts.[10]

Learning how to work in teams, brainstorming on issues, and networking with the right people can improve our individual practices. Publications based on multicentric research can provide data on comprehensive real-life effectiveness of various treatment strategies, especially in resource-poor regions where implementing strict guidelines may not be feasible. Innovations like using AI in Ophthalmology are made possible through collaboration among scientists, medical professionals, and technological experts. Thus, this concept needs to be nurtured and encouraged by all professional societies. Clarity and transparency in the collaboratorship process are essential in nurturing these networks and carrying them forward in future practice.

Signing off with best wishes to the incoming Editorial team ……

V Sudha

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Guest Editorial

Mucormycosis: An overview



ABSTRACT

Rhino-orbital mucormycosis is a life-threatening opportunistic fungal infection, which affects mainly immunocompromised hosts. It is commonly caused by ubiquitous fungi belonging to the order Mucorales, family Mucoraceae, which is also commonly known as the black fungus among the general population. The prevalence of mucormycosis (approximately 0.14 cases/1000 population) in India is about 80 times higher than in other developed countries. Despite aggressive treatment with surgical debridement and timely antifungal administration, the overall mortality rate is high. COVID 19 pandemic has led to an increase in the incidence of rhino-orbital mucormycosis. A multidisciplinary approach with early diagnosis and timely treatment with good control of glycemic levels, judicious use of steroids, and addressing immune status of patients helps in reducing the mortality and aids in improving survival rates of mucormycosis patients.

Keywords: Antifungal, COVID-19, immunocompromised, Mucorales, mucormycosis

INTRODUCTION

Rhino-orbital cerebral mucormycosis (ROCM) or phycomycosis is a life-threatening, angioinvasive disease caused by fungi of the order, Mucorales. It occurs mainly in immunocompromised conditions including patients with uncontrolled diabetes mellitus, hematological malignancies, postorgan transplant recipients on immunosuppressive therapy, and patients on iron overload therapy, hemodialysis, and chemotherapy who are at increased risk of acquiring mucormycosis.[1] It may also affect immunocompetent patients following trauma or burns.[2] Clinically classified as rhinocerebral, pulmonary, gastrointestinal, and disseminated. The incidence of mucormycosis has increased markedly in the settings of COVID-19 in India. It has been declared as an epidemic and a notifiable disease in many states.

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EPIDEMIOLOGY

The exact incidence of mucormycosis is unknown. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7/million population. The estimated prevalence of mucormycosis is 70% higher in India than in developed countries.[3] The high prevalence rate may be due to the increased presence of Mucorales in community, hospital environment, and immunocompromised state, especially uncontrolled diabetes. Association of COVID-19 with a recent increase in the incidence of mucormycosis is possibly due

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to severe acute respiratory syndrome coronavirus-2 causing impaired cell-mediated immunity and lymphopenia leading to a reduction in CD4 and CD8 cells.[4]

CAUSATIVE ORGANISMS

Mucorales are saprophytic fungi commonly found in decaying organic matter, soil, and air. Rhizopus, Lichtheimia, Cunninghamella, and Rhizomucor are the common pathogenic species causing mucormycosis in India. Rhizopus arrhizus, a nonseptae filamentous fungi, is the most common cause of mucormycosis in India. *Apophysomyces variabilis* is the second common isolated agent. Lichtheimia species contributes about 0.5% to 13% of cases from India.[5] Rare pathogens such as *Saksenaea erythrospora*, *Mucor irregularis*, and *Thamnostylum lucknowense* were also reported.[6]

RISK FACTORS

Mucormycosis is a rare disease, but several immunocompromised conditions can predispose it. Uncontrolled diabetes is the most common underlying risk factor for contracting mucormycosis and increases the severity of COVID-19. Hyperglycemia causes glycosylation of transferrin and ferritin and reduces iron binding which leads to increase in free iron levels. It enhances the expression of glucose-regulator protein78 of endothelial cells and Mucorales receptor core protein homologs, enabling angioinvasion, hematogenous dissemination, and tissue necrosis.[7] Severe neutropenia, steroid therapy, patients on prolonged ventilatory support, pulmonary tuberculosis, hematological malignancies, solid organ transplantations, malnutrition, autoimmune disease, HIV infection, and usage of immunosuppressant[8] drugs are the other important risk factors to be considered.

ETIOPATHOGENESIS

Saprophytic fungi are rapidly growing fungi, which release a large number of spores in the environment. Inhalation of sporangiospores by the hosts gets colonized in oral mucosa, nose, throat, and paranasal sinuses. In immunocompromised individuals, phagocytosis is impaired, thus fungal spores undergo proliferation with resultant angioinvasion. A rapid progression occurs which leads to pansinus involvement followed by the hematogenous dissemination to bony walls of the nose, palate, orbit, and finally to the brain resulting in extensive necrosis and tissue ischemia [Figure 1].

CLINICAL PRESENTATIONS

Generalized symptoms

a. Severe headache
b. Low-grade fever
c. Localized facial pain
d. Myalgia.

Ocular manifestations

a. Ocular pain
b. Periorbital edema
c. Proptosis [Figure 2]
d. Ptosis [Figure 3]
e. Diplopia
f. Ophthalmoplegia [Figure 4]
g. Discoloration of skin in the periocular region.
h. Numbness in the infraorbital region
i. Defective color vision
j. Sudden blindness due to CRAO, thrombosis of posterior ciliary arteries, infarction of the intraorbital part of the optic nerve, or direct fungal invasion of intracranial part of the optic nerve or optic chiasma[9] [Figure 5].

Nasal symptoms

a. Nasal block
b. Nasal bleeding
c. Blackish or blood-tinged nasal discharge
d. Post nasal drip.

Oral manifestations

a. Toothache, loosening of teeth
b. Loss of sensation or numbness over the hard palatal region
c. Blackish discoloration of buccal mucosa – Eschar formation [Figure 6]
d. Perforation over the palatal region.

Pulmonary manifestations

a. Fever
b. Cough with progressive dyspnea
c. Pleuritic chest pain.

Cutaneous and soft tissue manifestations

a. Erythema with induration
b. Black eschar at trauma/puncture site
c. Muscle pain.

Gastrointestinal manifestations

a. Fever
b. Bleeding per anus
c. Abdominal mass
d. Intestinal perforation.

Cerebral involvement

a. Altered sensorium
b. Hemiparesis
c. Seizures.

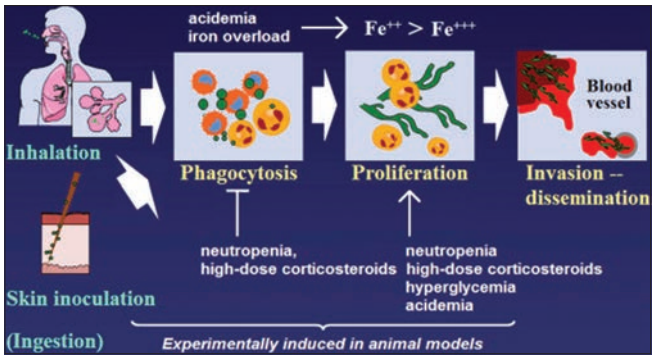


Figure 1: Pathogenesis of mucormycosis (Image courtesy: id.theclinics.com)



Figure 2: Left eye proptosis with chemosis



Figure 3: Right eye complete ptosis



Figure 4: External ophthalmoplegia

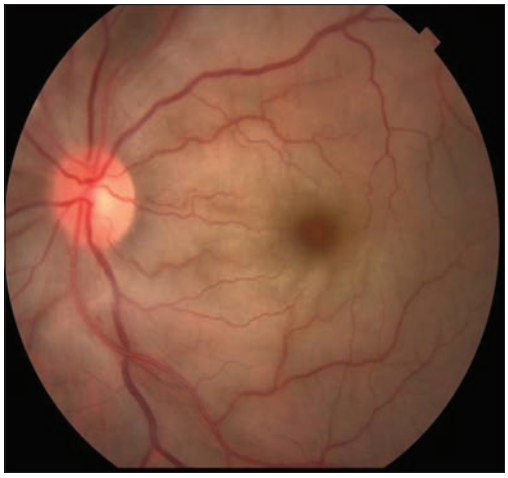


Figure 5: Fundus picture showing cherry red spot



Figure 6: Eschar over the hard palate

INVESTIGATIONS

Laboratory investigations include

1. Complete blood count
2. Blood sugar levels including fasting blood sugar, postprandial blood sugar, and HBA1C
3. Renal function test
4. Liver function test
5. Serum electrolytes
6. Serology–HIV, hepatitis B surface antigen, HCV
7. Serum ferritin.

HISTOPATHOLOGY AND DIRECT MICROSCOPY

Definitive diagnosis is achieved by the histopathological examination of the specimen collected by a high nasal swab or diagnostic endoscopy during the endoscopic sinus debridement of the involved tissue. The fungal invasion may be patchy, so multiple biopsies from the active areas of infection may be required. Microscopical analysis of the specimen using 10% potassium hydroxide mount shows nonseptate branched fungal hyphae branching at right angles[9] which provides presumptive diagnosis. Calcofluor white, Grocott-Gomori's methenamine silver, and periodic acid–Schiff are the special stains helpful in illustrating the presence and morphology of the fungus [Figures 7and 8].[10]

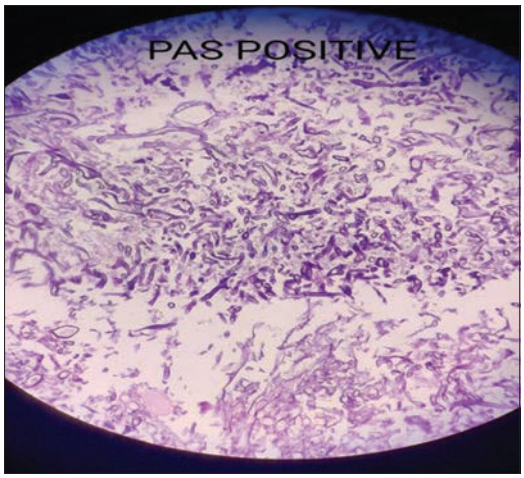


Figure 7: Periodic acid–Schiff stain highlighting the presence of branching hyphae

CULTURE

Surgically debrided or biopsied specimen should be cultured for the identification of the fungus to genus and species level and for antifungal susceptibility.

Specimens should be collected aseptically in sterile containers and transported to the laboratory within 2 h. Samples are cultured on Sabouraud dextrose agar without cycloheximide, brain–heart infusion agar, or potato dextrose agar. Fungal cultures should be examined twice weekly for 4 weeks before reporting it as negative. It usually takes 2–3 days for the colonies to appear. Identification is based on macroscopic dirty white, fluffy, cotton-like colonies and microscopic morphology and growth temperature which is usually 30°C and 37°C [Figure 9].

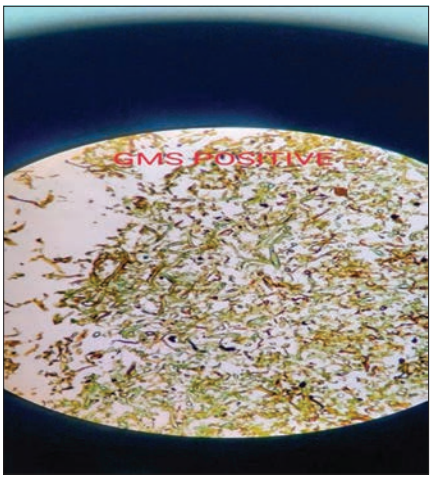


Figure 8: Grocott-Gomari's methenamine silver stain showing the invasion of mucor

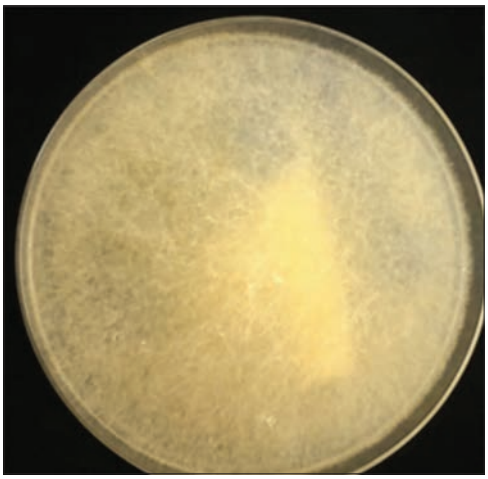


Figure 9: Culture plate showing dirty white, cotton-like colonies

IMAGING

Computed tomography (CT) and magnetic resonance imagining (MRI) help in the early diagnosis of ROCM. Imaging shows the changes proportional to the extent of the fungus invasion of the affected tissue.[11] CT scans demonstrate mucosal thickening and a lack of air–fluid level in the infected sinus in the early stages. In later stage, it demonstrates the destruction of the medial orbital wall and the rectus muscles invasion, orbital apex, and involvement of ipsilateral cavernous sinus.[12,13] Compared to CT scans, MRI allows for better visibility of orbital soft tissue invasion, infratemporal fossa involvement, intracranial structures, perineural invasion, and vascular obstruction.[14,15] Fungal elements in MRI cause low intensity due to mucosal involvement and lack of enhancement of the mucosa is caused by its angioinvasive nature. MRI variables such as T1- and T2-weighted images show devitalized mucosa appearing as contiguous foci of infection causing non-enhancing tissue, which appears as "Black turbinate sign."[16] In case of progressive ROCM disease, MRI shows hyperintense sinus wall, T2-W hyperintense

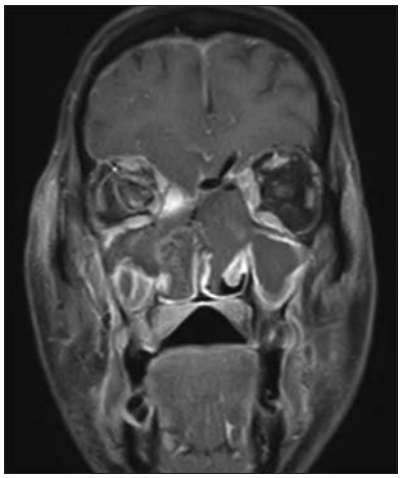


Figure 10: Image shows nonenhancing right inferior turbinate (black turbinate sign). Bilateral orbital cellulitis and focal cerebritis of basifrontal lobes (R > L) seen

lesion extending from paranasal sinus along orbital apex into intracranial structures, and narrowing or slow flow in the ipsilateral internal carotid artery [Figure 10].

DIAGNOSIS

Possible rhino-orbital cerebral mucormycosis

Patients with typical signs and symptoms with a history of COVID treatment, DM, on steroid therapy, supplemental oxygen, and ventilator support.

Probable rhino-orbital cerebral mucormycosis

Signs and symptoms along with diagnostic nasal endoscopy findings (or) contrast-enhanced MRI or CT.

Proven rhino-orbital cerebral mucormycosis

Clinicoradiological features along with microbiological confirmation (on direct microscopy) or culture/HPE/molecular diagnostics.[17]

STAGING

- Stage 1: Involvement of nasal mucosa
- Stage 2: Involvement of PNS
- Stage 3: Involvement of orbit
- Stage 4: Involvement of central nervous system (CNS).

MEDICAL MANAGEMENT

Rhino-orbital mucormycosis should be treated as an emergency without delay in initiation of therapy. Prompt antifungal administration, correction of underlying risk factor such as hyperglycemia, acidemia and aggressive surgical intervention is essential for good prognosis.[18]

INDUCTION THERAPY

- Drug of choice: Liposomal amphotericin B – Intravenous (IV) administration
- Dose for sino-orbital involvement – 5 mg/kg/day
- Dose for cerebral involvement – 10 mg/kg/day.

INJECTION MODE AND MONITORING

- Test dose: Injection liposomal amphotericin B 1 vial (50 mg) to be diluted in 12 ml of the diluent and 0.25 ml (1 mg) of solution made, to be mixed in 100 ml dextrose and to be infused in 30 min. Assessment for fever and allergic reactions is mandatory
- Prehydration: Five hundred milliliter normal saline administered over 30 min with 1 ampule (20 mmol) potassium chloride
- Therapy: 5 mg–10 mg/kg/day amphotericin B in 500 ml DS with 10 units of human insulin regular over 3 h
- Post hydration: Five hundred milliliter normal saline administered over 30 min.

After every dose of amphotericin B, renal function test with serum electrolytes has to be monitored.

If liposomal amphotericin B is unavailable, amphotericin B deoxycholate or amphotericin B lipid complex, which is less expensive can be used, but found to cause systemic toxicity.

In conditions where amphotericin is contraindicated

1. Isavuconazole IV 200 mg thrice daily for 2 days ->200 mg once from day 3 for 4–6 weeks (or)
2. Posaconazole IV 300 mg twice daily on day 1 – >300 mg once from day 2 for 4–6 weeks.

RETROBULBAR TRANSCUTANEOUS AMPHOTERICIN

Transcutaneous retrobulbar injection of amphotericin B

Injection into the retrobulbar space has been described as a minimally invasive, globe-sparing treatment for orbital mucormycosis.[19] Since lidocaine or bupivacaine is inflammatory, amphotericin B must be reconstituted with sterile water. Patients are anesthetized with a retrobulbar injection of 2–3 ml to avoid medication-induced pain. After 5 min, a 24-gauge retrobulbar needle was used to deliver 1 ml of liposomal amphotericin B to the retrobulbar space.[20]

Indications

The indications for retrobulbar injection are mild orbital involvement, patients presenting with ROCM with good vision acuity, without apical/CNS spread. It can also be administered along with IV amphotericin.

Dose
One milliliter of 3.5 mg/ml

Follow-up therapy
IV liposomal amphotericin B-5–10 mg/kg/day for a minimum of 4 weeks.

Step down therapy
IV isavuconazole 200 mg thrice daily for 2 days followed by 200 mg once from day 3 or IV posaconazole 300 mg twice daily on day 1 followed by 300 mg once from day 2 administered for 3–6 months (or) for a minimum of 6 weeks till evidence of clinical or radiological regression is noted.

SURGICAL MANAGEMENT

In case of predominant sinonasal with no (or) limited orbit involvement/vision preserved
Functional endoscopic sinus surgery is indicated to reduce the fungal load from the sinuses with irrigation with amphotericin B 1 mg/ml ± turbinectomy ± palatal resection ± medial orbital wall resection depending on the extension of the disease.

In case of disease progression, worsening of orbital component in <72 h
Orbital exenteration is indicated.

In limited central nervous system involvement
Orbital exenteration with aggressive debridement of paranasal sinuses ± turbinectomy ± palatal Resection ± orbital wall resection with clean margins is indicated.

In case of extensive central nervous system involvement
If systemic condition of the patient permits, orbital exenteration with aggressive debridement of paranasal sinuses ± turbinectomy ± palatal resection ± orbital wall resection with clean margins should be done.

PREVENTIVE MEASURES

a. Judicious and supervised use of systemic corticosteroids/tocilizumab
b. Aggressive monitoring and control of diabetes mellitus
c. Strict aseptic precautions while administering oxygen
d. Personal and environmental hygiene
e. Usage of clean distilled water for humidifiers during oxygen therapy
f. Administration of antibiotics/antifungals only when indicated
g. Do not neglect all cases with a blocked nose as cases of bacterial sinusitis, particularly immunocompromised patients and COVID-19 patients on immunomodulators
h. Clinical tests such as pupillary reaction, ocular motility, sinus tenderness, and palatal examination should be a part of routine physical evaluation of a COVID-19 patient.

CONCLUSION

ROCM is estimated to be high in India than in developed countries. In India, a large number of susceptible hosts are diabetics, a considerable number of patients are ignorant of their diabetic status and neglect regular health checkup.[1] Mortality associated with mucormycosis is noticeably high due to delays in diagnosing the disease and the challenges in managing the advanced stage of infection.

In COVID-19 pandemic outbreak, it is possible to decrease the incidence of morbidity and mortality due to mucormycosis by high index of suspicion and detailed evaluation, early diagnosis, reversal of underlying predisposing risk factors, aggressive surgical debridement,[8] and prompt antifungal therapy with effective multidisciplinary approach.

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Conflicts of interest
There are no conflicts of interest.

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Group practice – A concept doctors are shifting to

Treating a patient began by a single doctor at his premises as solo practice. After long years of its prevalence, the concept of group practice is now emerging, considering its many advantages. Now, many doctors are in group practice as it is an effective approach to face the sprouting demands of a progressively complex health-care scenario. Group practice is implemented as two or more doctors practicing under one roof as a single establishment.

There are five types of medical practice all over the world.[1]

SOLO PRACTICE

A single doctor treating his own patients at home or own/rented clinic with minimum support staff. This is also named as private practice. The advantages are individual freedom of treatment, maintenance of close relationship with patients, and liberty to set own working hours and holidays. New medical equipment can be purchased by the practitioner by choice for the growth of his practice. The disadvantages are long working hours, difficulty in availing long holidays as regular patients will suffer due to the practitioner's absence, and risks (financial or practice oriented) falling on the sole practitioner.

GROUP PRACTICE

A group practice involves two or more doctors who all will deliver medical care within the same facility. Group practitioners may be from a single specialty or multi-specialties. A group practice is established by the partner doctors agreeing upon terms of sharing the staff, income, and facilities available. Combined responsibility makes group practice less stressful. They will have more working capital compared to a single individual investing. The working hours, absence, and holidaying are all managed among the partners. The main drawback is the need for a consensus among doctors on business decisions and shared income.

HEALTH MAINTENANCE ORGANIZATION

The health maintenance organization (HMO) provides care only for their members and beneficiaries, for whom the association is formed. They will not treat an outside patient. It is aimed to reduce medical costs for their members. The two types of HMOs are staff model and group model. The benefits of employed doctors are stable work, regular hours, less regulatory responsibilities, regular salary, and bonus. Doctors working this way are disadvantaged with lack of autonomy and have to follow the organization's guidelines while treating a patient.

HOSPITAL BASED

A doctor is employed in a single- or multi-specialty hospital. The hospital will have a regular patient base and referral network. The advantages for a doctor in hospital-based practice are regular work schedule, low legal risk, and predictable income. The drawbacks are lack of autonomy and regulations of hospital committee.

LOCUM TENENS

In this modality, a doctor gets temporary employment at a specified place for a specified period. The salary may be high compared to permanent employment. The doctor employed in locum tenens is advantaged with schedule flexibility, variety, and different geographic locations. Regular transfer of working place, lack of steady work, and no additional benefits are the drawbacks.[1]

GROUP PRACTICE

History

Mayo Clinic, Rochester, Minnesota, USA, founded group practice in the late 1800s and is regarded as the father of group practice in medicine. Around 1932, there were 125 group practices. By 1980, group practice became a preferred model of practice in the USA. By 2011, group practice has become the accepted norm and main health-care system the world over.

Unity is strength transpires as the moto for group practice. Instead of a single mind, many minds work together for success here. The medical fraternity is gradually shifting from solo practice to group practice as this happens to be a safe mode of medical practice. The issues a solo practitioner faces are multiple such as complex government regulations, expensive instrumentation, and corporate entities buying

up practices and patients. While conceding the autonomy, the doctor in a group practice gains many benefits. They combine different skilled doctors at the same working area so that the patient needs not to be referred to different hospitals for complete cure. A doctor in a group can afford to handle sophisticated, highly necessary, and costly equipment. Group practice can cover a wider area, work in multiple locations, deal with more patients, and can be more profitable. While working in a group, you will be benefited by regular feedback from peers and coworkers. There will be commitment to one's ethical duties to protect patients and avoid conflict of interests. They will be having full-time administrator and office staff to take care of patient appointment scheduling, cash handling, accounting, dealing with government regulations, and doing the ministerial work connected with hospital maintenance. Group practice can have advantageous negotiations with insurance companies to get higher reimbursement rates. The group will see that you will be having more time for yourself, your patients, and your family. There is less likelihood of burnout in a group. Financial transparency will be one of the attractive sides of group practice.Group practice will become a part of the health-care system in future too. Group practice seems to have more strengths than weaknesses.

Table 1 depicts the pattern of types of medical practice.[2]

Developing a group

Group can be of a single specialty or multi-specialties. The main formats of group practices are as follows:

1. Proprietorship
2. Partnership – registered or unregistered. Will have unlimited liability
3. Limited liability partnership
4. Corporate – private limited (2–200) or public limited (7 to unlimited)
5. Trust/society.

The key issues to be planned after forming a group are as follows:

1. Budgeting on preliminary expenses, fixed cost, operating cost, and availability of finance and its cost.
2. Taxation like GST, income tax, asset purchase, foreign currency registration, and import/export code
3. Human resource issues – ESI, PF, and other statutory obligations.

Group practice can be started in a rented building or own premises. For having own area, the group has to purchase the land at the government or local body specified area. Then, plan the building design for a hospital and get the license from the local body or government. The next important duty is planning the workforce in addition to the group of doctors. The most important part is to get an idea from different sources by different members of the group on planning and purchase of different medical equipment. There should be facility for Electronic Medical Record section to collect, preserve, and retrieve the patient data on health and in disease. In present-day circumstances, there should be ways to promote ethical health-care marketing. Different strategies such as professional referral marketing, internet marketing, internal marketing, external marketing, public relations, and branding are the ways established and successful groups resort to without crossing lines drawn by the Ethics of National Medical Commission.

Table 1: Distribution of physicians by ownership status and type of practice (2021)

	Gender			Age		
Ownership status	All	Women	Men	Under 40	40 to 54	55+
Owner	53.2%	38.7%	59.6% [a]	43.3%	51.4% [a]	60.0% [a]
Employee	41.8%	55.7%	35.8% [a]	51.3%	44.2% [a]	34.7% [a]
Independent contractor	5.0%	5.7%	4.7%	5.4%	4.5%	5.3%
	100%	100%	100%	100%	100%	100%
Type of practice						
Solo practice	18.4%	21.0%	17.3% [a]	10.0%	15.8% [a]	25.3% [a]
Single specialty group	45.5%	39.7%	48.0% [a]	46.2%	46.7%	43.8%
Multi-specialty group	22.1%	23.0%	21.6%	27.0%	21.6% [a]	20.3% [a]
Direct hospital employee	5.6%	5.7%	5.6%	9.3%	6.3% [b]	3.1% [a]
Faculty practice plan	2.7%	2.3%	2.9%	2.4%	3.4%	2.2%
Other [2]	5.7%	8.2%	4.6% [a]	5.2%	6.3%	5.3%
	100%	100%	100%	100%	100%	100%
N	3466	976	2490	724	1747	995

The smooth running and success of a group practice depends on different factors and responsibilities of each member of the group. Due respect to everyone in the institution is a must. Learn from experienced sources on how to do and how not to do things. Be honest in your approach and do what benefits the entire group. Do not go for short-term benefits at the cost of others. Arrive at a partnership agreement and set rules of engagement of each partner. The group should have a written business plan. Select the most suitable doctor as a leader with another doctor as a leader in the wings to assist and learn from. Have frequent board meetings to form an opinion and support the decisions of board always. The group has to add the right doctors and facilitate a smooth exit for wrong doctors from the group.[3] There should be no poaching of patients. Transparency in accounting makes sharing of profits easy. Allow each doctor to customize aspects such as consulting hours, holidays, vacation, and role in management of the institution or in research as far as possible. Build up camaraderie among the group by staying together, working together, playing together, and holidaying together.

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Conflicts of interest

There are no conflicts of interest.

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Asymptomatic Goldenhar syndrome in an adult

A 60-year-old elderly female presented to our clinic for routine examination. There was no significant past history. Snellen's best-corrected visual acuity in both eyes (BE) was 6/6 with − 2D sphere. Intraocular pressure by noncontact tonometry was 14 mmHg in the right eye (RE) and 16 mmHg in the left eye (LE). Slit lamp examination in the RE revealed upper lid [Figure 1a] coloboma with papilloma [Figure 1b] and early cataract. Slit lamp evaluation in the LE revealed small temporal whitish elevated epibulbar dermoid abutting the limbus at 3'O clock [Figure 1c] with early cataract. Fundoscopy was within normal limits in BE. General examination revealed preauricular appendages on both the ears [Figure 2a and b]. Looking at the clinical picture, a diagnosis of Goldenhar syndrome (GS) with lenticular myopia was made.[1] As the patient was happy with her vision, she was advised best-corrected glasses and observation for GS.

CLINICAL SIGNS

- Eyes: Microphthalmia, epibulbar dermoids/limbal dermoids, lipodermoids, and coloboma
- Ear: Anotia
- Face: Marked facial asymmetry with unilateral macrostomia, aplasia, or hypoplasia of the mandibular ramus and condyle may be seen. Hypoplasia of the zygomatic area
- Skeletal alterations: Cranium bifidum, microcephaly, dolichocephaly, plagiocephaly, spina bifida, hemivertebrae, butterfly, fused, and hypoplastic vertebrae like vertebral anomalies have been seen
- Other systems: Anomalies affecting trachea, lung, heart, kidney, and gastrointestinal systems
- Seen in children: Congenital anomaly of mesoblasts giving rise to branchial and vertebral anomalies.[2]

DESCRIBED BY

- 1861 – Classical features seen by Canton and then 20 years later by Von Arlt

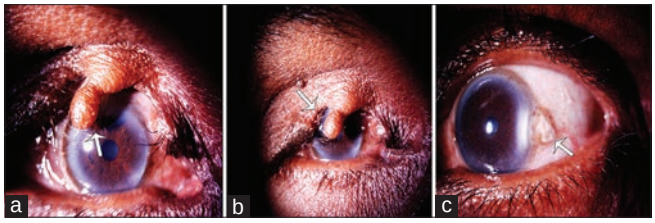


Figure 1: (a) Image of the right eye depicting upper lid papilloma with skin tag suggestive of Goldenhar syndrome (b) Image of the right eye depicting upper lid coloboma (c) Image of the left eye depicting temporal epibulbar epidermoid

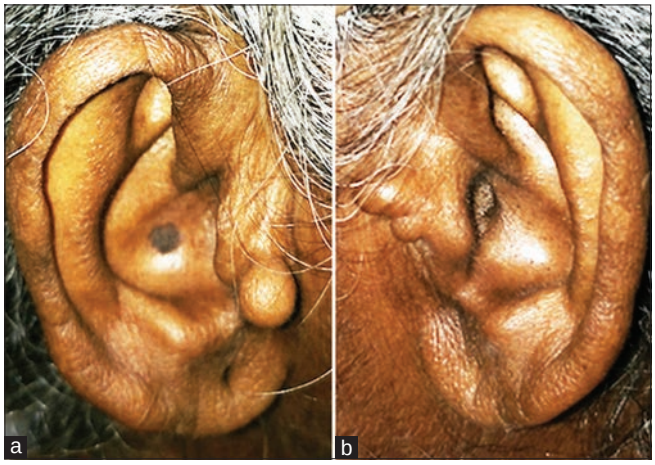


Figure 2: (a) Image of the right ear depicting preauricular appendage (b) Image of the left ear depicting preauricular skin appendage

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- 1952 – Goldenhar recorded hemifacial microsomia and epibulbar dermoids
- 1963 – Gorlin *et al*. suggested the name occulo-auriculo-vertebral dysplasia
- 1978 – Smith used the term facio-auriculo-vertebral sequence to include both hemifacial microsomia and GS.

Why it occurs?

Various hypotheses are:

1. Gorlin and Pindborg hypothesized that an unknown primary cause of faulty embryological development causes abnormality of the mesoblasts giving rise to branchial and vertebral anomalies
2. Jong Bloet suggested that the syndrome was a result of fertilization of overripe or aged ovum
3. Recent accepted theory states imbalance in cells during the blastogenesis period (30–45 days of intrauterine life) of embryo formation. It is found to involve the derivatives of the first and second branchial arches.[3]

What else to examine?

Multisystem examination to rule out

1. Treacher Collins syndrome –similar features with a bilateral presentation
2. Townes–Brocks syndrome shows thumb anomalies, anal defects, and renal anomalies which are not seen in GS
3. Linear nevus sebaceous of Jadassohn depicts cloudy cornea, warty cutaneous lesions, infantile spasms not seen in GS
4. CHARGE syndrome – characteristic semilunar canal anomalies and cranial nerve dysfunctions while mandibulofacial dysostosis can be differentiated by esophageal atresia and microcephaly.[3]

Take home message

1. GS in an adult has rarely been reported[4]
2. Patients in various age groups can have varied manifestations as phenotype can vary greatly in its severity depending on the activation and expression of the defective gene
3. Asymptomatic cases of GS can be observed.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Major Review

Rhino-orbito-cerebral mucormycosis in COVID 19 patients: Understanding the pathophysiology

ABSTRACT

The pandemic caused by severe acute respiratory syndrome coronavirus 2 has had health implications of unprecedented magnitude. The second wave of the pandemic hit India with a tremendous rise in the number of patients requiring care not only for the viral inflammatory disease but also for secondary infections. Nearly 6–7 new patients of rhino-orbito-cerebral mucormycosis with active or resolved COVID-19 infection are reporting daily at a tertiary institute in Northern India. This another battle against an epidemic of mucormycosis, within an already established ongoing war of COVID-19 pandemic has aroused a need to understand the causal factors and implement effective prevention and control programs. The authors performed a thorough literature review in PubMed to understand the correlation between the two diseases. This review summarizes the plausible risk factors, and environmental determinants of mucormycosis in COVID-19, that are of particular importance to public health professionals.

Keywords: Black fungus, COVID-19, mucormycosis, ROCM

INTRODUCTION

As the second ripple of the COVID-19 pandemic touched India, the nation documented a record number of new COVID-19 cases in the 1st week of May 2021. Amid this chaos, a new epidemic of rhino-orbito-cerebral mucormycosis or popularly called "the black fungus," emerged. Nearly 6–7 new patients of rhino-orbito-cerebral mucormycosis with active or resolved COVID-19 infection are reporting each day at a tertiary eye care institute in Northern India. Even though the second wave of the pandemic has started showing a gradual reduction, alarmingly, the number of mucormycosis cases is increasing daily. Therefore, there is a need to understand the pathophysiology behind the development of mucormycosis infection among these patients.

METHODOLOGY

To understand disease pathogenesis, the authors conducted a two-step literature review. The first search was performed in PubMed using the keywords "Mucormycosis," "pathogenesis," "rhino-orbito-cerebral mucormycosis" and "*Rhizopus*." The search was limited to the last 3 decades (1990–2020). Studies, reviews, systemic reviews, meta-analysis, and case reports with significant data were included. The authors noted that the major risk factors for the development of Mucormycosis were found to be diabetes, immunocompromised state, solid organ transplant, and hematopoietic stem cell transplantation.

The authors then conducted a second stage literature review, using the keywords "immune response," "COVID 19," "Diabetes," "Rhino-orbito-cerebral mucormycosis," "invasive

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fungal disease," "novel coronavirus 2019," "SARS COV 2," "solid organ transplant," "stem cell transplantation." The search was limited to December 2019 to May 2021. Studies, reviews, systemic reviews, meta-analysis, and case reports with significant data were included.

RESULTS

After, performing the literature review, the authors were able to formulate certain patient-related factors, few virulence factors of certain species of the fungus and some sources of infection which could attribute to the development of the disease.

PATIENT-RELATED FACTORS

Mucormycosis is one of the most rapidly progressive invasive fungal infections affecting human beings. Although the fungi can be found everywhere in nature; it rarely affects normal individuals.[1,2] The disease most commonly is seen in diabetics, immunocompromised hosts, patients with leukemia, lymphoma, multiple myeloma, multiple blood transfusion, septicemia, hepatitis, cirrhosis, renal failure, and patients on chemotherapy or steroids. In the past, diabetes was considered to the most common associated systemic illness; however, due to the progress in knowledge pertaining to the treatment, presently immunocompromised state secondary to chemotherapy has become the commoner systemic association in European and North American developed countries.[3,4] In developing nations such as India, the prevalent association still remains diabetes.[5] Rhino-orbito-cerebral mucormycosis is the most common form of mucormycosis and seen particularly in cases of uncontrolled diabetes mellitus[6] [Figure 1].

Diabetes in COVID-19

Diabetes being a chronic inflammatory disease process hinders the normal response of the body to a pathogen. Hyperglycemia leads to oxidative stress and causes tissue inflammation by upregulating the production of pro-inflammatory cytokines, and adhesion molecules.[7] Inadequately controlled high blood sugars have also been linked to abnormal lymphocyte proliferative response to stimuli, unusual monocyte/macrophage reaction, and impaired neutrophil response.[8,9] Patients with COVID-19 infection may have preexisting diabetes or latent diabetes mellitus, making them susceptible to the disease.[10] However, contrary to the popular belief that an individual acquires diabetes following high doses of steroids, the statement may not be completely correct. A COVID-19 patient can develop diabetes by any or combination of the following ways:

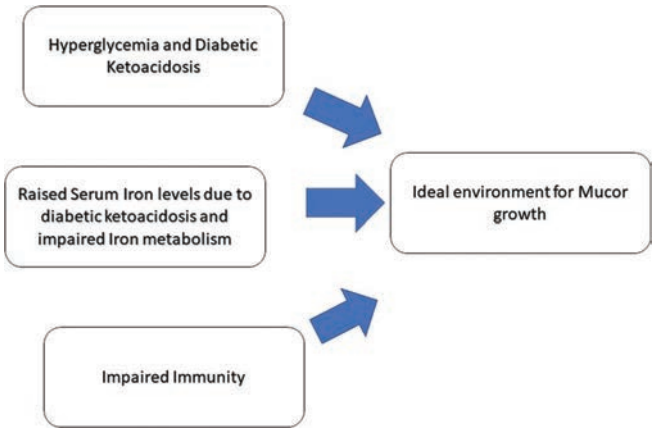


Figure 1: Plausible risk factors creating a conducive ideal environment for mucor growth

Pancreatic beta-cell damage by a direct viral invasion of the islets

Angiotensin-converting enzyme (ACE) 2 receptors are present in the lungs and are known to be associated with the cellular entry of COVID-19.[11] Studies have shown that both the exocrine glands and beta cells of the pancreas express a larger number of ACE 2 receptors than the lungs. In a retrospective study of 121 COVID 19 patients, elevated serum amylase and lipase levels were noted primarily in severe COVID 19 patients indicating damage to the pancreas.[12,13] Another study by Yang *et al*. revealed patients with COVID 19 infection developing acute diabetes after acquiring the viral disease.[14] Therefore, the virus can directly invade the pancreas and lead to the acute onset of diabetes [Figure 2].

Other than the ACE 2 receptor, transmembrane protease serine (TMPRRSS) 2, a protease enzyme, also partakes in the cellular entry of the virus. Studies involving human lungs with camostat mesylate, a TMPRRSS blocker has shown decreased severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) infection.[15] The same TMPRRSS receptor has also been found in gastrointestinal tissues, namely the stomach, pancreas, liver, and intestine. COVID-19 infection can cause hyperglycemia by acting directly on these receptors located in pancreatic tissues.[15-17]

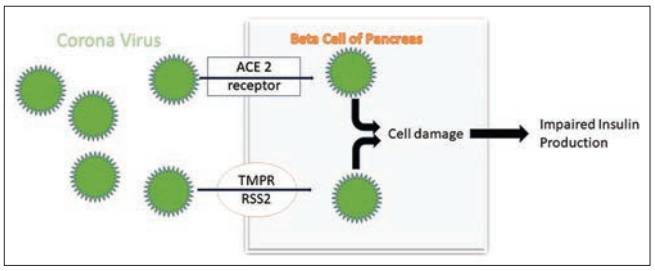


Figure 2: Pancreatic beta-cell damage by a direct viral invasion of the islets

Insulin resistance from severe inflammation

COVID-19 infection is associated with high levels of inflammatory mediators, procalcitonin, ferritin, interleukin-6 (IL-6), and C-reactive protein being the more common ones.[18-20] Accumulation of innate immune cells complexes in tissues results in the release of inflammatory mediators such as IL-6 and transforming growth factor-α.[21] These inflammatory mediators can themselves lead to damage of beta cells of the pancreas by converging on various signaling molecules as JUN kinase, inhibitor kappa B kinase β, and nuclear factor-κB and even directly stop the action of insulin by phosphorylating insulin receptor substrates 1 and 2[21,22] [Figure 3].

Glucocorticoids

As mentioned earlier, during COVID-19 infection, the human body undergoes a sudden surge in inflammatory mediators. The virus after entering the respiratory epithelial cells invokes a sudden production of cytokines in large quantity along with a weak interferon response. Membrane-bound immune receptors mediate the pro-inflammatory response of T-Helper 1 cells, CD 14+ CD16+ monocytes. Macrophages and neutrophils reach the respiratory epithelial cells and the inflammatory event follows.[23] The surge often termed as cytokine storm, requires immediate control, for which glucocorticoids are used routinely.[23,24] Glucocorticoids in the form of methylprednisolone as well as dexamethasone have been proven to reduce the risk of death in severe COVID-19 cases.[25-27] However, a high dose of glucocorticoids themselves can lead to diabetes by causing varying degrees of beta-cell dysfunction, insulin resistance, and insulin release. Yasuda *et al*. have demonstrated the reduction of binding affinity of insulin due to the use of hydrocortisone, prednisone, and dexamethasone.[28] *In vitro* studies of glucocorticoids on the beta-cell function of cultured rat insulin-secreting insulinoma, has revealed an impaired insulin release following glucocorticoid usage.[29]

Phosphoenyl pyruvate carboxykinase (PEPCK) is known to regulate glyceroneogenesis in the liver and adipose tissues. However, in the presence of glucocorticoids, the PEPCK gene is suppressed leading to inhibition of glyceroneogenesis. This results in an increase of fatty acids in the blood which interferes with glucose uptake and insulin resistance.[30]

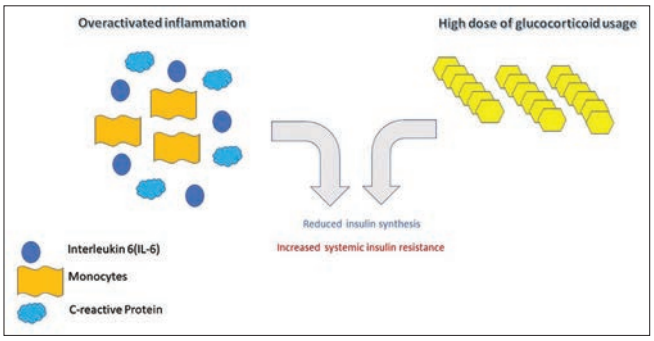


Figure 3: Insulin resistance from severe inflammation

Multiple studies are there which has documented steroid-induced hyperglycemia in hospitalized patients with or without preexisting diabetes.[31-33] Xiao *et al*. have reported 34.7% cases developing steroid-induced diabetes in patients who received steroids in SARS in 2004.[34] We have also come across several patients developing steroid-induced diabetes for which both oral hypoglycemics and insulin was needed to control hyperglycemia.

Impaired defense mechanisms against mucor

Mucormycosis is commonly found in patients with impaired function of phagocytes.

The complement system is an integral component of humoral immunity. They help in the opsonization and phagocytosis of macrophages via macrophages and neutrophils. Diabetes is known to be associated with reduction of Complement factor 4 (C4) leading to impaired action of the polymorphonuclear dysfunction and reduced cytokine response.[35,36]

Hyperglycemia also blocks glucose-6-phosphate dehydrogenase and increases apoptosis of polymorphonuclear leukocytes.[36] In tissues that do not depend on insulin for glucose transport, a hyperglycemic environment leads to raised glucose levels within the cell. These tissues utilize nicotinamide adenine dinucleotide phosphate (NADPH) for the metabolism of the excess glucose causing depleted levels of NADPH making the tissues prone to oxidative stress.[36]

Neutrophils play an important role in the inhibition of fungal proliferation. In chronic diabetes and diabetic ketoacidosis, where there is low pH, phagocytes become dysfunctional, leading to impaired chemotaxis and defective intracellular killing of hyphae.[37]

Iron availability

Mucor requires iron for its cell growth and development.[38] In SARS CoV 2 infection the iron metabolism is greatly affected. In the initial stages, the innate immune system takes control of the iron metabolism and restricts iron absorption by raising the hepcidin levels. Consequently, the serum iron levels decrease.[39]

However, once diabetic ketoacidosis sets in, there is an increase in free iron levels in serum. The acidotic environment disrupts the binding of transferrin to free iron by proton mediated pathway.[40]

Zinc is a micronutrient which is responsible for maintaining tissue barrier such as the respiratory epithelium. In addition to its barrier function, it also participates in redox reaction and is an essential component for working the immune system. It is believed to reduce the progression of COVID 19 infection.[41] Zinc has been therefore overtly used in the management of COVID 19. Zinc and Iron are known to compete for metabolic processes due to their relatively similar physico-chemical properties, therefore a sudden rise in Zinc levels can lead to increased iron availability.[42]

Rhizopus oryzae expresses gene encoding high-affinity iron permease (FTR-1), which produces redundant surface reductases involved in free iron assimilation by reductive pathway. Heme also acts as a source of iron for *Rhizopus*, expressing heme oxygenase enzymes. This probably explains the angio-invasive nature of organisms for obtaining iron from host hemoglobin. Rhizoferin, a siderophore secreted by *Rhizopus*, also supplies iron through a receptor-mediated pathway[40] [Figure 4].

Role of glucose regulated protein 78

Glucose regulated protein 78 (GRP78) is a cellular protein belonging to the HSP70 protein family that is mainly present in the endoplasmic reticulum. Its main function is involved in protein folding and assembly, acting as a chaperone protein. However, in a variety of cells, it is translocated to the cell surface, where it acts as a receptor for Mucorales, helping in penetration and damage to endothelial cells.[43] GRP78 is overexpressed in cases where serum glucose and iron are elevated, like diabetic ketoacidosis.

VIRULENCE FACTORS

Cunninghamella species have been identified to have more than twice the mortality rates compared with *Rhizopus* species. Inherently greater resistance to antifungal agents and polymorphonuclear leucocyte-mediated hyphal damage likely contributes to poorer outcomes. *Rhizopus* secrete certain enzymes like aspartic proteinase, which helps in increased cell lysis, and have an active ketone reductase system, which helps in active proliferation in ketoacidosis states.[44]

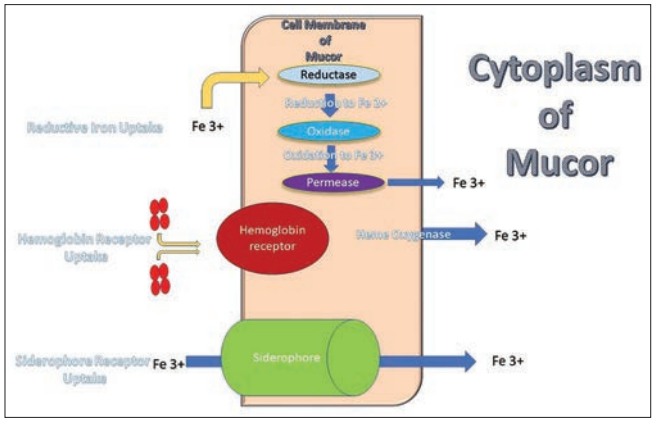


Figure 4: Iron uptake in mucorales

SOURCE OF MUCOR INFECTION

Hospital

The exact transmission of mucormycosis still remains a mystery. The popularly accepted notion is that the fungi inoculate the nasal mucosa, after which it spreads to the nasal sinuses and the orbit, eventually advancing to the cranial cavity.

Hospital at times serves as a possible source of infection. In the 1970s an outbreak of mucormycosis cases was noted in multiple hospitals of America, where eventually elasticized bandages were found to be contaminated with *Rhizopus*. The manufacturer implemented necessary hygienic guidelines which lead to a decrease in the number of cases.[45,46] Osteotomy bags were responsible for a cluster of 2 cases of mucormycosis in 2005. The gum used in the bags were made from the sap of a tree, which was recognized as the source of the fungus.[47] Similarly, osteotomy bags have been found to spread the infection in a premature infant and in an adult with renal insufficiency.[48,49] Wooden tongue depressors were responsible for mucormycosis infection in 4 premature infants while being used as a splint for intravenous cannulation site.[50] Intravenous and intraarterial catheters, urinary bladder catheters and even thoracic drains have also been noted to act as a source of mucormycosis infection.[51-53] Adhesive tapes, adhesive urine bag, temperature probe, skin patch for testing hypersensitivity all have been implicated in cutaneous mucormycosis cases.[54-57] Bed linens, insulin infusion pumps, prosthetic valves, and nasal packings have also been described as the source in many cases.[58]

Environment

Other than Hospitals, the disease has been also found to occur near construction sites. Cluster cases of pulmonary mucormycosis have been documented in the literature.[59,60]

Possible preventive measures from developing Mucor

The majority risk for developing mucor are patients with diabetes, COVID-19 infection and steroid use. Stringent protocols should be followed by hospitals and institutions starting steroids in COVID-19 patients, especially those with preexisting diabetes. Strict glycemic control should be maintained with oral hypoglycemic agents and insulin injections. As the number of patients is rising due to

pandemics, paramount importance should be given to following infection control protocols at the hospital level. Timely identification of nosocomial outbreaks and pseudo-outbreaks is critical in curbing the disease and starting antifungals to reduce mortality and morbidity associated with the disease.

Voriconazole has been used as a prophylactic antifungal in stem cell recipients, but there was the incidence of breakthrough mucormycosis. This was probably due to an increase in virulence of fungus following exposure to voriconazole. In patients with prolonged neutropenia, organ transplant, graft versus host disease, or history of mucor, Posaconazole can have been proven to be beneficial as a prophylactic drug. However, care should be taken by monitoring serum levels to identify adequate absorption and compliance since low levels have an increased risk of breakthrough mucormycosis. Isavuconazole has also shown its efficacy as a prophylactic drug in cases of hematologic malignancies.[61] Patients with high-risk features should be advised to maintain healthy living practices and avoid activities leading to trauma or exposure to fungal spores.

CONCLUSIONS

Mucormycosis in COVID 19 is a life-threatening condition. Although clinical reports are abundant and the clinical manifestations of mucormycosis have been extensively described, the pathogenetic basis of the disease is only recently becoming clearer. The development of the disease revolves around the hyperglycemic state of the patients. Patients with neutropenia, diabetic ketoacidosis, and those on deferoxamine therapy are at increased risk of developing mucormycosis. The angioinvasion and pathology in various organs, in the at-risk host, is a result of the virulence factors involved in the host-pathogen interaction.

A better and clearer understanding of the predisposing conditions and host defenses, thereby their correction and augmentation, respectively, with counteracting the virulence of mucor, will furnish promisable outcomes with resultant reduction of morbidity and mortality.

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Conflicts of interest
There are no conflicts of interest.

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The validation of questionnaires

ABSTRACT

We have previously described the design and development of a questionnaire. It is important to establish the validity of a questionnaire before it is administered to a population. A series of inter-related tests are required to determine the validity of a questionnaire. Questionnaires pass through an iterative process that includes the development of items, testing of the validity, revision of items, revision of the conceptual basis of the test, retesting, and repetition of the process till the questionnaire is finalized. The process of validation of a questionnaire continues if the questionnaire is in use. In this manuscript, we briefly describe the conceptual basis of the different methods that are used to establish the validity of questionnaires and item retention and exclusion.

Keywords: Internal consistency, item response theory, questionnaire, validation

INTRODUCTION

Validity refers to the interpretations of measurements and is fundamental to the development and interpretations of tests.[1,2] A questionnaire (or scale or test) has a specific purpose. The interpretations of the scores or results of the questionnaire must relate to the specific purpose of the questionnaire.[1-3] Validity provides a quantitative description of the support provided by evidence and theory to the interpretation of test scores.[1-3]

Structural validity

The scale or questionnaire generally follows one of three models.[4-6] The most common model is a quantitative model that uses the levels or degree of the target construct to differentiate individuals.[4-6] The other models include class models that categorize individuals into qualitatively different groups and the more complex dynamic models.[4-6] The structural validity implies that the internal structure of the questionnaire parallels the external structure of the target condition and reflects the underlying variance.[4,7] Structural validity includes empirical assessments based on nontest parameters, tests for internal consistency focused on inter-item and item-total measures, and item response theory (IRT) assessments based on latent traits. Empirical assessments are useful at the stage of questionnaire development although they are usually used in external validation these days. Empirical assessments include the administration of the item pool to a clinical and community sample.[2,8] The differences in mean item scores are then used in conjunction with other parameters to determine inclusion or exclusion of an item.

Internal consistency is widely used in the development of a questionnaire. Item-total correlations are generally used to determine if an item must be retained or excluded and can be done when developing a single scale.[1,9,10] However, an exploratory factor analysis (EFA) is a better and preferable option if the questionnaire has hierarchical constructs or multiple constructs. The EFA helps to identify the underlying dimensions (unidimensional or multidimensional) that are subsequently used for scale construction. The initial step is a principal factor analysis or a principal component analysis. Items that have loading factors 0.35–0.40 and items

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that have similar or stronger loadings on other factors are eliminated from the item pool of questions.[11-13] Confirmatory factor analysis is then used to further explore the structural validity of the questionnaire.[1,11-14] The loading of items in the factor analysis is used to explore the redundancy or similarity of items and the correlation of the items with the theoretical basis of the questionnaire and other items in the questionnaire.[1,9-14]

The IRT is another method that can be used after EFA to assess structural integrity, especially in short-form questionnaires.[10,15,16] IRT presumes that each item response reflects an underlying construct. IRT also presumes that an item characteristic curve can describe the item–trait relationship as a monotonically increasing function. IRT tries to identify specific items that provide maximum information for everyone and based on their level of the underlying dimension. IRT considers an item as optimal if the respondent has a 50% probability of responding correctly. IRT is also used to estimate item difficulty and item discrimination. The ability to estimate the individual item–trait level without administering a fixed set of items is a major advantage with IRT.[16,17] This allows the development of computer-aided tests (CATs) that can be scaled up in difficulty based on the underlying capability of the person and through a subset of items that are maximally informative for each person. CATs are equally efficient and can provide trait-level information using fewer items than a conventional questionnaire.[16,17]

Evaluation of the psychometric properties

The development of the questionnaire may lead to a revision of the theoretical concept underlying the questionnaire like how individual items are revised.[1,9,11] An initial step is to examine the response distributions of individual items. Items that have a highly skewed distribution (floor and ceiling effects) or questions where most respondents provide a similar response must be considered for elimination.[1,9,11] These unbalanced questions provide little information, weakly correlate with other items, and lead to highly unstable correlational results.[1,9,11]

The next step is to determine the items to eliminate or retain in the questionnaire. Each item in the questionnaire should measure only one thing.[1] However, we must look at the differences between internal consistency and unidimensionality. Internal consistency describes the intercorrelations between items of a scale. Cronbach's coefficient alpha is a test that is commonly used to determine internal consistency with a threshold of ≥0.80 suggesting that the item can be retained.[18-20] Unidimensionality indicates whether the items in a scale assess a single underlying factor and is, therefore, a better measure of the validity of a questionnaire.[21,22] The often-used Cronbach's coefficient alpha is of limited use in the determination of unidimensionality. The Cronbach's coefficient alpha is also a function of the scale length and average inter-item correlation (AIC) and can lead to an imperfect measure of internal consistency.[18,22] Several highly correlated items, many moderately correlated items, and various combinations of scale length and AIC can lead to erroneous measures of internal consistency using Cronbach's alpha test.[18,22] Cronbach's alpha test cannot be used if the number of items in a questionnaire is more than 40.[1,18,22]

An AIC that falls between 0.15 and 0.5 is considered a better measure than the Cronbach's coefficient alpha.[21,22] However, the AIC alone cannot establish the unidimensionality of the questionnaire. A higher AIC can be obtained by averaging many higher coefficients with many lower ones. It is, therefore, necessary to examine the range and distribution of these correlations and not focus only on the AIC.[21,22] Thus, the AIC and majority of the inter-item correlations should range between 0.15 and 0.50 to ensure unidimensionality.[1,21,22]

External validity

The process of external validation of a questionnaire continues if that questionnaire is in use. Clear conceptualization of the theory, development of specific and relevant item pools, and assessment of convergent and discriminant validity during the scale development help to understand what the questionnaire measures and what it does not.[1]

Convergent validity is examined by assessing the relationships between indicators of the same construct.[23] Discriminant validity examines the relation of a measure with indicators of other constructs and looks to establish that highly correlated constructs within hierarchical models are empirically distinct from one another. Discriminant validity is established by showing that convergent correlations are significantly higher than discriminant coefficients.[1,23] Criterion validity is shown through the significant relation of a test with theoretically relevant nontest outcomes (e.g., clinical diagnoses and arrest records). Incremental validity demonstrates that the measure adds significantly to the prediction of a criterion over and above what can be predicted by other sources of data.[23]

CONCLUSION

The design, development, and validation of a questionnaire involves several stages of testing and revision to establish validity. Changes to the structure of the questionnaire in terms of addition or deletion of questions, rewording

questions, and change in response scales affect the validity of the questionnaire and impact on the interpretation of results. Questionnaires are developed for specific contexts in specific populations. It is important to retest the validity of a questionnaire when it is applied in a new context or a different population or when a translated version of the questionnaire is used.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Ocular morbidity due to the usage of handheld digital devices: A population-based cross-sectional study using a validated questionnaire

ABSTRACT

Purpose: To study the ocular morbidity exclusively due to the usage of handheld digital devices (HHDD). **Materials and Methods:** It is a population-based cross-sectional study using survey method. A questionnaire was prepared, and face validity was established. Pilot study with 25 participants was used to validate the questionnaire. Data were collected from 534 participants and data of 207 participants were excluded from the analysis based on the exclusion criteria. Thus, data of 327 participants were considered for the analysis purpose. Data set was divided into two depending on whether the participant used HHDD for 2 h on a day or more. Then these two groups were compared regarding the ocular morbidities. Data were analyzed using SPSS 26.0 version. **Results:** Out of 327 participants, 181 participants (55.4%) were males and 146 participants (44.6%) were female. Eye strain ($P = 0.0252$), Neck pain ($P = 0.0006$) and Watering of eyes ($P = 0.0069$) had statistically significant association with the usage of HHDD. Participants who use HHDD for more than 2 h/day were at 1.95 times of higher risk and participants with continuous usage of HHDD for >2 h/day were at 1.86 times higher risk of getting ocular morbidities than others. In HHDD users asthenopic symptoms were more compared to ocular surface-related problems. **Conclusion:** This study demonstrates that the long and continuous usage of HHDD has a significant association with ocular morbidity. Further studies are needed to analyze and ascertain whether the existing treatment algorithm and ocular ergonomics for computer users are enough for individual or combined usage of HHDD.

Keywords: Computer vision syndrome, handheld digital devices, ocular morbidity

INTRODUCTION

Digital devices (DD) has become an integral part of our life owing to their ever-increasing significance in making our life easier. Most used DD are mobile phones, computers (desktops and laptops), E-Readers, Game consoles, etc.[1] DD could be broadly classified into two types – hand held DD (HHDD) which are usually used within 30 cm from the eye and non HHDD (NHHDD) which are used at a distance of more than 30 cm from the eye.[2]

Digital eye strain (DES) is a condition characterized by visual disturbance, ocular discomfort caused by DD. Symptoms of DES include ocular fatigue, watering of eyes, blurring of vision, burning sensation, redness, and double vision.[3] The prevalence of DES is estimated to range from 20% to 90% among visual display unit users.

Due to the recent technological advancements, HHDD are able do most of the things previously done by NHHDD. This would have a profound effect on ocular health, in general, owing to the significant reduction in the distance from the eye to the screen. Most of the initial research in relation to

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the usage of DD were based on computers (NHHDD). HHDD differs from computers in many parameters like viewing position and distance, font size, luminance, pattern of use, etc.[4] Hence, there can be a difference in the morbidity profile of HHDD in comparison to NHHDD. Thus, it is important to exclusively study the ocular morbidity profile of HHDD, to design specific ergonomic practices and treatment protocols. The authors evaluated available literature for the effects of HHDD on binocular vision, blinking, and ocular surface to consider potential aetiologies.

MATERIALS AND METHODS

Study population

The general population above 15 years of age willing to participate in the study were considered irrespective of their nativity, race, or gender.

Study design

Population-based study using a validated survey questionnaire

The sample size was calculated using the formula

$$n = \frac{Z^2_{1-\alpha/2} p(1-p)}{d^2} \quad (1)$$

where $Z_{1-\alpha/2} = 1.96$

p = Expected proportion

d = Absolute precision.

The sample size obtained was –310

Inclusion criteria

Participants from the general population who voluntarily filled the questionnaire.

Exclusion criteria

- Participants under the age of 15
- Participants who were using computers for more than 2 h a day.

Data were collected using an online questionnaire with 13 multiple choice questions related to the usage of the DD. The questionnaire was circulated in social media and the resulting data maintained in a spreadsheet.

Validation of the questionnaire

Validation of questionnaire was done by 6 step validation method.

1. Face validity of the questionnaire was established by 2 independent evaluators-a subject expert and a statistician. They ensured that the survey does not contain any errors such as leading, confusing, or double-barrelled questions
2. Pilot study was done using 25 participants
3. Data obtained in a spreadsheet was checked for any inconstancies
4. Principal components analysis (PCA) was done to identify underlying components and themes that are being measured by survey questions. Kaiser-Meyer-Olkin Measure of Sampling Adequacy value obtained was 0.62. Since the PCA value was above 0.6, it was accepted
5. Internal consistency was checked by the test-retest method. Done with 50 participants and the reliability of the questions were established by statistical analysis
6. Revision of the questions and extension of the survey was done.

The data collected from the patients were recorded and analyzed. Descriptive analysis of the population's characteristics was carried out. Categorical variables were expressed as counts and percentages. Univariate analysis using Chi-square test was done to find out the association between the various determinants of different kinds of morbidities. Data set was divided into two depending on whether the participant used HHDD for 2 h on a day or more. Then these two groups were compared regarding the ocular morbidities. Odds ratio and 95% confidence interval were measured. Data were analyzed using IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp [Table 1].

RESULTS

Demographic characteristics of the population

534 participants enrolled in the study out of which those who use laptops or desktops for more than 2 h were excluded. Data from the remaining 327 participants was analyzed. 181 participants (55.4%) were males and 146 participants (44.6%) were females. 152 participants (46%) were of the 26–35 years age group. 195 participants (59%) had any one of the ocular morbidities studied.

Participants in the age group 26–35 years constituted 47% of the morbidity reported. Among the participants with morbidities 59% were male and 41% were female. The maximum number of participants had neck pain (20%) followed by eye strain or fatigue (19%). 73% of the participants with morbidities were using HHDD for more than 2 h a day [Table 2].

About 48% of the participants with morbidity were not aware about the type of screen available in their HHDD. 27% of

Table 1: Validated questionnaire

1. Age group: (a) 15-25 (b) 26-35 (c) 36-45 (d) 46-55 (e) 56-65 (f) 66-75 (g) Above 75
2. Sex: (a) Male (b) Female (c) Other
3. How long are you using HHDD: (a) <2 years (b) 24 years (c) 46 years (d) 68 years (e) Above 8 years
4. Daily usage of all type of HHDD in hours: (a) 0-1 h (b) 1-2 h (c) 2-4 h (d) 4-6 h (e) Above 6 h
5. Purpose for which HHDD is maximum used on a daily basis: (a) Work, browsing, chatting, reading, social media use (b) Watching movies, videos (c) Playing games
6. Commonly used brightness level in HHDD: (a) 0%-25% (b) 25%-50% (c) 50%-75% (d) 75%-100%
7. Type of screen in your HHDD: (a) TFT LCD (b) IPS LCD (c) OLED (d) AMOLED (e) Super AMOLED (f) E ink (g) Don't know
8. Do you have any of the following problems while using HHDD: (a) Blurring of vision (b) Pain in eyes (c) Redness of eyes (d) Head ache (e) Watering of eyes (f) Eye strain or fatigue (g) Burning sensation (h) Neck or shoulder pain (i) None of the above
9. Do you commonly use HHDD continuously for more than 2 h: (a) Yes (b) No
10. Daily usage of desktop and laptop in hours: (a) 0-2 h (b) 2-4 h (c) 4-6 h (d) Above 6 h (e) Not using
11. Purpose for which desktop and laptop is maximum used on a daily basis: (a) Work, browsing, chatting, reading, social media use (b) Watching movies, videos (c) Playing games
12. Do you have any known eye disease: (a) Short sight or long sight (b) Glaucoma (c) Retinal or nerve diseases (d) Eye injuries (e) Cataract (f) Squint (g) Other (h) None
13. Are you using a spectacle with anti-glare protection: (a) Yes (b) No

HHDD Hand held digital devices, TFT – Thin Film Transistor, IPS – In Plane Switching, LCD – Liquid Crystal Display, OLED – Organic Light Emitting Diode, AMOLED – Active Matrix Organic Light Emitting Diode

Table 2: Sub group analysis

Determinant	Level	Yes, *n* (%)	No, *n* (%)	OR (95% CI)	*P*
Duration of HHDD usage (years)	>6	117	90	0.700 (0.439-1.114)	0.132
	≤6	78	42		
Daily usage of HHDD (h)	>2	144	78	1.950 (1.2193.132)	0.0053*
	≤2	51	54		
Purpose	Watching movies, videos, playing video games	38	20	1.355 (0.7489-2.4531)	0.315
	Work, browsing, chatting, social media, reading	157	112		
Brightness level (%)	050	144	95	0.996 (0.3564-2.7883)	0.9952
	75100	11	8		
	5075	40	29		
Continuous usage of HHDD >2 h	Yes	71	31	1.865 (1.1348-3.0666)	0.0139*
	No	124	101		
Spectacles	Yes	58	31	1.365 (0.82292.2665)	0.2279
	No	137	101		

*Statically significant association. HHDD Hand held digital devices, OR – Odds ratio, CI – Confidence interval

the participants with morbidity were using HHDD with LCD screens [Figure 1]. Among the participants with morbidities 45% of them had refractive errorr as a co-morbidity.

Participants with cumulative HHDD use for >2 h/day were at 1.95 times of higher risk and participants with continuous usage of HHDD for >2 h/day were at 1.86 times higher risk of getting ocular morbidities than others.

The usage of HHDD for more than 6 years showed an increase in morbidities, although the *P* value is not statistically significant. 80% of the participants with morbidities used HHDD for working and social media usage. Eye-related problems were more prevalent among those who used HHDD for working and reading than those who used it for watching videos and playing games. 63% of the participants in the study were using HHDD with a brightness <50%. Those participants who were using HHDD at a reduced brightness level (0–50%) had more morbidities than the others though the *P* value is

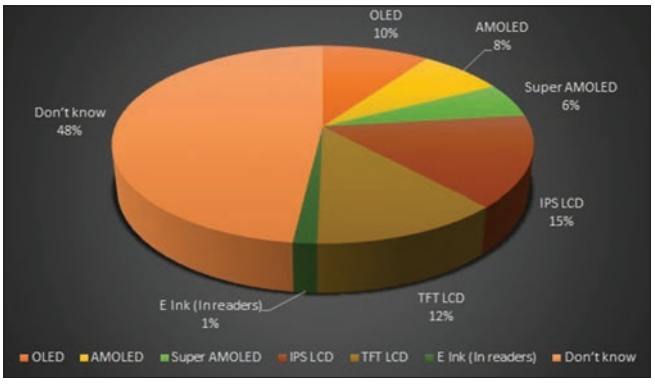


Figure 1: Pie chart comparing screen type versus ocular morbidities

not statistically significant. Usage of protective spectacles did not show any association to ocular morbidities.

Participants who use HHDD for more than 2 h were at 2.23 times of higher risk of having eye strain or fatigue compared to those who use HHDD for <2 h. Participants who

use HHDD for more than 2 h were at 3.51 times of higher risk of getting neck or shoulder pain compared to those who use HHDD for less than 2 h [Table 3]. Participants who use HHDD for more than 2 h were at 5.31 times of higher risk of getting watering in the eyes compared to those who use HHDD for <2 h. These 3 symptoms had a direct causative association with usage of HHDD which was statistically significant 0.20% of those with morbidities had shoulder pain and 18% had eye strain or fatigue [Figure 2].

DISCUSSION

Demographic features

Analysis of 327 participants were made and 152 (46%) participants were in the age group of 26–35 years. 181 (55.4%) participants were males and 146 (44.6%) were females. 195 (0.59%) participants had either one of the ocular morbidities. Maximum morbidity (47%) seen in the age group 26–35 years.

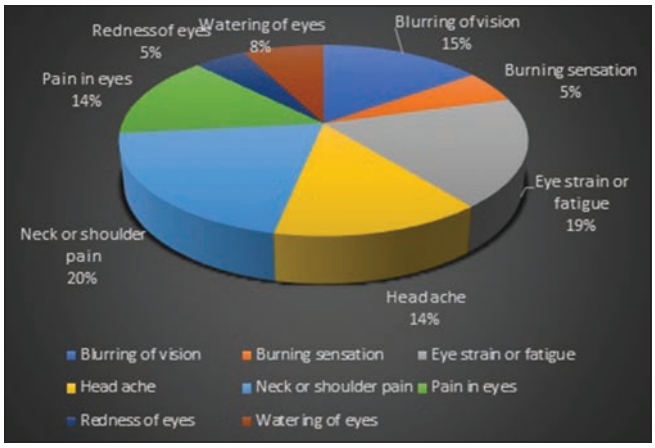


Figure 2: Pie chart showing incidence of ocular morbidities (%)

The usage of smartphones is more in younger age groups and according to a study by Coles-Brennan *et al*. younger individuals do more complicated tasks in smartphones. This may be a cause for more symptoms in the younger age groups.[5]

Hand held digital devices and asthenopic symptoms

When the symptomatic profile of HHDD users were analyzed, greater number of participants were having asthenopic symptoms compared to ocular surface-related symptoms. According to Jaiswal *et al*. HHDD has short viewing distance, small font size, which can cause more asthenopic symptoms. Furthermore, smartphone and tablet use results in reduced fusional convergence and possibly a receded near point of convergence which can result in a greater incidence of asthenopic symptoms. Reddy *et al*. in their study in university students found out that 19.7% had head ache and 16.4% had irritation while using DD.[6] 20% of the participants were having neck or shoulder pain. According to Al-Khlaiwi and Meo people tilt their heads at odd angles, or they bend toward the screen to see it clearly.[7] These postures can result in muscle spasms or pain in the neck or shoulder.

Hand held digital devices and ocular surface symptoms

Among the participants with morbidities ocular surface symptoms were less compared to asthenopic symptoms. According to Jaiswal *et al*. the available literature does not conclusively link visual discomfort symptoms or reduced blink rate with HHDD use.[4] Moon *et al*. did a study on primary school children in Korea and found that the dry eye symptoms were directly proportional to mobile phone usage.[8]

Participants who were using HHDD for more than 6 years had more ocular symptoms. Participants who used

Table 3: Analysis of ocular morbidities

Determinant	Cumulative daily usage of HHDD (h)	Yes, *n* (%)	No, *n* (%)	OR (95% CI)	*P*
Blurring of vision	≥2	25	197	1.084 (0.5122.297)	0.8323
	<2	11	94		
Burning sensation	≥2	15	207	7.536 (0.981957.839)	0.052
	<2	1	104		
Head ache	≥2	36	186	1.500 (0.74553.0181)	0.2557
	<2	12	93		
Eye strain or fatigue	≥2	46	176	2.233 (1.10484.5151)	0.0252**
	<2	11	94		
Eye pain	≥2	33	189	1.4921 (0.72203.0833)	0.2799
	<2	11	94		
Neck or shoulder pain	≥2	60	162	3.518 (1.71997.1981)	0.0006**
	<2	10	95		
Watering of eyes	≥2	30	192	5.312 (1.582817.8313)	0.0069**
	<2	3	102		
Redness of eyes	≥2	10	212	1.6038 (0.43205.9538)	0.4803
	<2	3	102		

**: Statistically significant association, HHDD Hand held digital devices, OR – Odds ratio, CI – Confidence interval

HHDD >2 h a day as well as its Continuous usage both showed increase in ocular morbidity. Ranasinghe *et al*. reported that the visual symptoms increased significantly in individuals who spent >4 h daily working on video display terminals.[2] According to AOA, symptoms occur because the visual demands of the task exceed the visual abilities of the individual to comfortably perform the task.

Participants using HHDD for watching videos and playing games was observed to be negligible in the study population. According to Parihar *et al*. watching videos and playing games needs more of binocular functions, accommodation, and convergence which can result in more ocular morbidities.[9] For conclusive evidence, we need studies with equal participation from all three groups. Participants using HHDD with LCD screens were found to have more mordidity than the others. Even though both LCD and LED are liquid displays, LEDs can be dimmed dramatically improving the picture quality due to high contrast ratio and may reduce the ocular symptoms.

Those participants who were using HHDD at a reduced brightness level (0–50%) had more morbidities than those using higher brightness levels. According to Jaiswal *et al*. it is advisable to adjust screen brightness to match the level of surrounding light.[4] In this study 30% of the participants used various types of protective glasses and it had no significant correlation to eye symptoms. According to Johansen *et al*. blue light cutting spectacles helps reduce exposure to Blue Light emitted from DD.[10]

Future dimensions of the study

The specific symptomatology due to the usage of HHDD was analyzed in the study. Comparative studies between the users of HHDD and Computers should be encouraged to differentiate the symptomatic profile of both and to understand the cumulative effects of their simultaneous usage. The higher incidence of asthenopic symptoms in HHDD usage warrants the development of ergonomic practices specifically for HHDD users. The various adjustments in HHDD like brightness, screens, and protective glasses should be studied thoroughly to minimize ocular morbidity.

What was known

1. The usage of tablets and mobile phones may cause ocular symptoms
2. A wide variety of screens are available for hand held devices like LCD, LED, OLED etc.
3. Antiglare and blue cut spectacles are available in the market to protect eyes during usage of DD
4. Ocular comorbidities may increase the incidence of ocular symptoms in DD users
5. Those who are using DD can have DES.

What this study adds

1. Longer duration (>2 h) and continuous usage (>2 h) of HHDD usage causes asthenopic symptoms more than ocular surface-related symptoms
2. Usage of HHDD with LCD screens may cause more ocular symptoms in comparison to LED screens
3. Protective spectacles may not necessarily reduce ocular symptoms in HHDD users
4. Refractive error is the co-morbidity that is most associated with ocular symptoms while using HHDD
5. Visual morbidities due to HHDD and NHHDD can have difference in their morbidity profiles with HHDD users having more of asthenopic symptoms.

CONCLUSION AND RECOMMENDATIONS

The continuous and constant usage of HHDD can induce ocular symptoms which has a specific profile and it may be different from the extensively studied one for computer vision syndrome (CVS). In our study of HHDD usage, we could demonstrate that Asthenopic symptoms had a significant causative association when compared to ocular surface symptoms.

Focused study examining different ocular protection features, ambient room brightness, and light reflection metrics is required to ascertain specific features of HHDD induced ocular symptoms and to establish control factors which could differentiate with the existing studies related to the usage of CVS. Further research is needed for better understanding symptoms and etiology to develop treatment algorithms and ocular ergonomics specifically made for HHDD users.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Central corneal thickness, anterior chamber depth, and axial length in patients with type II diabetes mellitus

ABSTRACT

Purpose: The aim of this study was to study the central corneal thickness (CCT), anterior chamber depth (ACD), and axial length (AL) in patients with type II diabetes mellitus and compare it with healthy controls. **Methods:** A hospital-based nonrandomized prospective comparative study was conducted on 50 type II diabetics and 50 healthy controls. Complete ophthalmic examination was performed. CCT was measured using an ultrasound pachymeter, ACD, and AL was measured using an optical biometer. Statistical comparisons were done between the cases and controls. **Results:** The mean CCT in diabetic group was significantly higher (531.00 ± 33.42 μm) compared to control group (505.70 ± 32.19 μm) ($P < 0.001$) The mean ACD in diabetics (3.19 ± 0.35 mm) was significantly lesser compared to healthy control (3.78 ± 0.10 mm) ($P < 0.001$). CCT and ACD values between subgroups of diabetics such as duration of diabetes, grade of retinopathy, HBA1C values were statistically not significant ($P > 0.05$). AL s were comparable between the two groups. **Conclusion:** Patients with type 2 diabetes mellitus in our study had a thicker CCT and shallow anterior chamber regardless of retinopathy status, duration of diabetes mellitus, glycemic control.

Keywords: Anterior chamber depth, axial length, central corneal thickness, diabetes mellitus

INTRODUCTION

Diabetic keratopathy is a known entity that affects approximately 70% of diabetic population and includes decrease in corneal endothelial cell density (CED) and hexagonality, polymegathism, pleomorphism, increase in CCT, higher corneal autofluorescence, and lower corneal sensitivity.[1,2] Central corneal thickness (CCT) is an important measurement for the diagnosis, treatment, and management of various ocular conditions and also a sensitive indicator for endothelial physiology and functions.[3,4] CCT has a positive correlation with intraocular pressure (IOP) measured by Goldmann Applanation tonometry and this effect on measured IOP can be clinically significant.[5] Thicker CCT in diabetes mellitus should be taken into consideration while measuring IOP in diabetics.

Diabetic subjects are at higher risk of glaucoma.[6] Diabetes can decrease anterior chamber depth (ACD).[7,8] which can be a predisposing factor for the development of angle-closure glaucoma. Measurement of ACD acts as a valuable tool for the prediction and diagnosis of primary angle-closure glaucoma.[9] Diabetes also has a positive association with open-angle glaucoma.[6,10] and may affect axial length (AL) and spherical equivalent.[11-13] Short AL has been associated with diabetes[14] and diabetic retinopathy.[12] This study was conducted to assess the corneal thickness, ACD, and AL in diabetic subjects and compare it with that of healthy controls.

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MATERIALS AND METHODS

This prospective, hospital-based, comparative study protocol was approved by the university's institutional ethical committee. Our study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients before their enrolment in this study. The diagnosis of Diabetes mellitus was based on the criteria of the American diabetic association (ADA).[15] Recruitment of the subjects was based on medical history and treatment taken by the patients attending the outpatient department. Nondiabetic patients taken as controls underwent two random blood glucose tests in accordance with the recommendations of the ADA[15] to disclose undetected diabetes.

The inclusion criteria for the study are patients willing to give written informed consent, patients age >40 years, patient's diagnosed as type II diabetes at least 1 year before the study, and started on antidiabetic drugs. The exclusion criteria included patients not willing to give written informed consent, postoperative patients, patients with corneal diseases and dystrophies, type I diabetes, contact lens users, any ocular trauma such as blunt and penetrating injuries, history of any other systemic illness, patients with glaucoma and retinal diseases not associated with diabetes, any other ocular diseases such as dry eye, anterior uveitis, primary angle-closure glaucoma, evidence of any corneal pathology on slit-lamp biomicroscopy and high refractive errors. For standardization, the right eye of all the subjects was examined. The patient was positioned on a chair in front of the devices till the instruments automatically took an image of various parameters mentioned above. The ocular examination included slit-lamp anterior segment examination, grading of the lens nuclear sclerosis (according to Lens Opacity Classification System III), IOP was measured using Goldmann applanation tonometer, dilated fundus examination using slit-lamp biomicroscopy (90D), indirect ophthalmoscopy, and fundus photography if required. Subjects were examined using optical biometer (Tomey OA-2000) for ACD, AL measurement, and noncontact specular microscope Tomey EM– 4000 (Tomey Corporation, japan) for CCT measurement.

Sample size estimation-Based on a previous study by Ozdamar *et al*.[16] the difference in means of CCT was 26 and standard deviation of cases was 30 and standard deviation of controls was 35, with the alpha error being 0.01 and the power of study 90% (beta error– 0.10), the minimum number of sample required in each group would be 50.

The sample size was calculated using Med CalcVersion 14.8-1993-2014, Med calc software bvba.

Statistical analysis: The data were analyzed using the statistical package for social sciences (SPSS 17 version) (SPSSINC., 233 South Wacker Drive, 11th floor, chicago). The normal distribution of variables was assessed using the Kolmogorov–Smirnov test ($P < 0.05$ indicated that the data were not normally distributed). Results were presented as mean ± standard deviation, median and interquartile ranges are presented for parameters (CCT, ACD, AL). Repeated analysis of variance was used for comparison of the mean. A-scan biometry between the case and control, the association between the various parameters were studied using linear regression analysis. $P < 0.05$ was considered significant.

RESULTS

In this study, 50 type II diabetic cases were compared with 50 healthy controls. The mean age of all recruited patients was 56.36 ± 9.66 years. Table 1 details the distribution of cases and controls with respect to age, gender, IOP, HbA1C. The mean CCT in diabetics 531 (±33.42) μm was significantly thicker than the CCT of healthy controls 505.70 (±32.19) μm ($P < 0.01$). CCT was increased in cases with diabetes more than 11 years however this was not statistically significant ($P = 0.808$) as represented in Table 2. Table 3 details the mean anterior ocular segment biometry between the groups. The mean ACD in diabetics was 3.19 (±0.35) mm compared to 3.78 (±0.10) mm in healthy controls, the difference was statistically significant ($P < 0.001$). The AL between the two groups, diabetics, and healthy

Table 1: Distribution of subjects with respect to age, gender, intraocular pressure, and random blood sugar

Characteristics	DM (*n*=50)	Non-DM (*n*=50)
Age, mean±SD	57.62±9.09	55.10±10.130
Gender, *n* (%)		
Male	16 (32)	24 (48)
Female	34 (68)	26 (52)
IOP, mean±SD	13.21±2.81	13.5±2.02
RBS, mean±SD	276.76±119.2	141.50±23.49

n - Number of eyes included in each group. DM - Diabetes mellitus, IOP - Intraocular pressure, RBS - Random blood sugar, SD - Standard deviation

Table 2: Comparison of central corneal thickness with duration of diabetes

Duration (years)	*n*	Mean±SD	ANOVA *F*	*P*
≤5	22	527.86±29.88	0.214	0.808 (NS)
6-10	18	532.00±36.18		
≥11	10	536.10±38.37		
Total	50	531.00±33.42		

SD - Standard deviation, ANOVA - Analysis of variance, NS - Not significant

Table 3: Comparison of mean anterior ocular segment biometry findings between the groups

Descriptive statistics	Groups	*n*	Mean±SD	50th (median)	Minimum	Maximum	Interquartile range		*t*	*P*
							25th	75th		
CCT (um)	Cases	50	531±33.42	530.50	431.00	581.00	488.75	559.00	3.855	<0.001
	Control	50	505.70±32.19	510.00	441.00	572.00	482.75	530.25		
ACD (mm)	Cases	50	3.19±0.35	3.16	2.57	3.95	2.96	3.47	11.44	<0.001
	Control	50	3.78±0.10	3.78	3.55	3.97	3.71	3.87		
AL (mm)	Cases	50	22.72±0.84	22.65	21.35	24.88	22.16	23.20	1.396	0.166
	Control	50	22.95±0.81	23.34	21.34	24.90	22.34	23.45		

P<0.05 (significant). *n* - Number of eyes examined in each group. CCT - Central corneal thickness, ACD - Anterior chamber depth, AL - Axial length, SD - Standard deviation

controls were comparable. IOP, CCT, ACD, and AL between subgroups of diabetics such as duration of diabetes, IOP, Hemoglobin A1C (HbA1C) values were statistically not significant ($P > 0.05$). Table 4 gives the coefficients from linear regression analysis between age, sex, duration, HbA1C with IOP, CCT, ACD, AL in cases. Lens sclerosis was significantly associated with ACD. Tables 2 and 5 represent the comparison of CCT with the duration of diabetes and HbA1c levels respectively.

Table 4: Linear regression analysis between age, duration, sex, hemoglobin A1c (independent variables) with intraocular pressure, central corneal thickness, anterior chamber depth, axial length (dependable variables) in cases

Model	*t*	*P*	*R*	Adjusted R^2	*P*
Dependent variable: IOP					
1					
Constant	3.142	0.003	0.304	0.012	0.348
Sex (1=male, 0=female)	−1.165	0.250			
Age	1.551	0.128			
Duration	−0.078	0.938			
HbA1c	−0.475	0.637			
Dependent variable: CCT					
1					
Constant	14.311	0.000	0.410	0.094	0.077
Sex (1=male, 0=female)	2.159	0.036			
Age	−1.632	0.110			
Duration	0.885	0.381			
HbA1c	−0.762	0.450			
Dependent variable: ACD					
1					
Constant	7.374	0.000	0.160	−0.061	0.879
Sex (1=male, 0=female)	0.634	0.529			
Age	0.090	0.929			
Duration	0.894	0.376			
HbA1c	−0.070	0.945			
Dependent variable: AL					
1					
Constant	22.886	0.000	0.463	0.145	0.025
Sex (1=male, 0=female)	3.160	0.003			
Age	1.495	0.142			
Duration	0.726	0.471			
HbA1c	1.009	0.318			

CCT - Central corneal thickness, ACD - Anterior chamber depth, AL - Axial length, IOP - Intraocular pressure, HbA1c - Hemoglobin A1c

DISCUSSION

Diabetic keratopathy implies spectrum of changes occurring in the cornea of diabetic patients. In our study, patients with type 2 diabetes mellitus had a thicker cornea and shallow anterior chamber that had no association with duration of the disease, diabetic retinopathy, or glycemic control.

The relation between CCT and diabetes mellitus has been reported differently in various studies. In our study, we found that diabetic patients had significantly thick corneas than nondiabetics. Reduction of Na + K + ATPase activity due to increased sugar levels directly inhibits the corneal endothelial pump function increasing stromal hydration and intracellular accumulation of sorbitol, an osmotic agent causes corneal hydration in diabetics.[17] Recent studies suggesting advanced glycosylated end product acting as cross-linking agents to increase the covalent bond in the corneal stroma and eventually its thickness and gradual stiffening of the cornea and consequently affect the accuracy of IOP measurements.[17]

Many studies have showed diabetics to have increased CCT.[16,18-20] However, in a study conducted by Inoue *et al*.,[21] Wiemer *et al*.[22] CCT in diabetic patients was comparable with that of nondiabetic patients.

In our study, we found that ACD in diabetes was shallower compared to the controls which was similar to the study by Saw *et al*.[7] where cases with diabetes had shallower anterior chambers and thicker lenses (4.88 vs. 4.75 mm, $P = 0.003$). Reduction in ACD in diabetes patients supports the concept that the disease may be a risk factor for the development of acute angle closure.[14]

Increasing lens thickness and decreasing ACD in diabetics have been confirmed in a population-based twin study and it was also found that ACD was negatively correlated with

Table 5: Comparison of central corneal thickness with hemoglobin A1c values

HbA1c	*n*	Mean±SD	ANOVA *F*	*P*
≤7	5	530.00±22.93	0.053	0.948 (NS)
8-10	21	529.38±33.00		
≥11	24	532.63±36.55		
Total	50	531.00±33.42		

SD - Standard deviation, HbA1c - Hemoglobin A1c, NS - Not significant, ANOVA - Analysis of variance

the duration of diabetes.[14] Although we did not observe any correlation between the duration of the disease and anterior segment parameters, diabetics had a significant association of lens thickness with the IOP and ACD. Measurement of ACD in diabetics may aid in the early detection and management of angle-closure glaucoma. In our study , there was no significant influence of HbA1c levels on central corneal thickness, anterior chamber depth and axial length , parameters being mentioned in Table 5.

Pierro *et al*.[12] in their study showed that diabetic patients presented shorter ALs compared with the controls. Significantly shorter ALs were found in the background and proliferative retinopathy groups compared with the group without retinopathy and no difference in AL was found between the diabetic patients without retinopathy and the on diabetic subjects. In our study, AL measurements were comparable between the two groups. The absence of association of the anterior segment parameters with duration and glycemic status needs further evaluation as the changes in diabetics could be a transient phenomenon occurring during increased blood sugars.

Limitations of this study included (a) Myopic and hyperopic refractive shifts in diabetic patients which have been related to changing plasma glucose concentration could not be assessed as refractive values were not taken into account. (b) CCT was taken into account while peripheral corneal thickness was not, hence the need for further studies measuring both the corneal thickness. (c) Effect of diurnal variation on CCT due to variation of plasma blood glucose levels was not assessed. (d) Only right eye being considered for measurements in this study, possible interocular differences in the parameters could not be accounted for.

CONCLUSION

Thicker central cornea and shallow anterior chamber were found in patients with diabetes mellitus than that of healthy controls. CCT is pivotal in refractive surgeries, glaucoma workup, donor tissue evaluation before keratoplasty, and long-term contact lens users. A simple noninvasive test in form of pachymetry helps in the identification of those patients with diabetes who could be at higher risk of developing ocular complications, enabling better control of disease. A shallow anterior chamber seen in diabetes can be used as a screening tool in the diagnosis of angle-closure glaucoma.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Multidose bevacizumab (Avastin) vial microbial safety: A real-life scenario

ABSTRACT

Purpose: The purpose of the study is to evaluate the microbiological safety profile of multidoses of bevacizumab (Avastin) from a single-use vial in a real-life scenario. **Methods:** In a prospective interventional study, a total of 12 sequential vials of bevacizumab (Avastin) were used for this study. After using each vial for multipuncture, multidoses of intravitreal injections for 1 month, leftover bevacizumab in the vial was again stored in the refrigerator at 4 C. All the vials were sent for microbiological evaluation using Gram staining, potassium hydroxide mount, blood agar, MacConkey agar, and brain–heart infusion broth cultures; both at the opening of each vial and after utilization of 12th vial. Patients receiving intravitreal injections from these vials for various ophthalmic indications were followed up at least 3 months postprocedure for clinical evidence of infection. The Microbiology Laboratory is standardized, especially for ophthalmology specimens, and the media, blood agar and MacConkey, agar were prepared in-house, whereas brain–heart infusion broth is commercial media (HiMedia). **Results:** All the 12 used vials' microbiological evaluation when evaluated at the opening of vials and 13th month of the study period showed no bacterial or fungal elements. None of the patients who received intravitreal injections from these vials developed clinically detectable ocular infection or inflammation. **Conclusion:** This study suggests that the contents of multiple-dose bevacizumab (Avastin) vials remain sterile over a period of 1 year without any microbial contamination if proper refrigeration and aseptic precautions are maintained. Multipuncture, multidose Avastin vial utilization with due aseptic precautions and storage shows reliable microbiological safety both *in vitro* and *in vivo* over 1 year period.

Keywords: Avastin, bevacizumab, multidose, refrigeration, sterility

INTRODUCTION

Bevacizumab (Avastin) is a recombinant monoclonal antibody approved by the Food and Drug Administration (FDA) for the intravenous treatment of colorectal cancer.[1]

Its off-label intravitreal use has shown promise for the treatment of proliferative diabetic retinopathy and iris neovascularization.[2,3]

Bevacizumab is available in a vial containing 100 mg in 4 ml solution and one needs only 0.05 ml for intravitreal injection that accounts to 1.25 mg which is commonly used in an ophthalmology practice. It was reported that anti-VEGF activity of bevacizumab which was left in the vial followed by refrigerating may degrade minimally over 6 months.[4] However, its sterility after multipuncture multidosing utilization has not been determined.

The current practice related to storage of bevacizumab vials is to aliquot and store in 1 ml plastic syringes for intravitreal injections whenever needed which is best done by compounding pharmacy.

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However, such facility is not available in all ophthalmic setups. Many other alternatives are being used which include either (1) pooling the patients in a given day and usage of single vial of bevacizumab by puncturing multiple times; (2) aliquoting without using the standards of compounding pharmacy; (3) using single vial of bevacizumab until the drug in it gets completely exhausted.

This study is carried out to know the microbial safety of Avastin vials (with multipuncture multidose utility) which were stored in refrigeration and re-used for 1 month each.

METHODS

A prospective interventional, single-center study was conducted over a period of 15 months (July 2018 till September 2019). Patients requiring intravitreal Avastin injections for various ocular conditions as diabetic macular edema, macular edema secondary to venous occlusion, and choroidal neovascular membrane were included in this study after obtaining informed consent. Institutional ethics committee approval was taken.

A total of 12 sequential vials of bevacizumab (Avastin) were used for this study. First, vial was opened in July 2018 (1st study month). Each time, the vial was punctured with 27G needle and tuberculin syringe; the rubber cap of the vial was wiped by isopropyl alcohol, allowed to dry, and disinfected with 10% povidone iodine. Prior utilizing each vial for intravitreal injections, bevacizumab drug from Avastin vial was drawn into tuberculin syringe with aseptic precautions and sent immediately to microbiology laboratory for bacterial and fungal cultures, Gram staining, and potassium hydroxide (KOH) mount. All the vials were always returned to the refrigerator and stored at 4°C at procurement, in between the procedures and the period after utility till the 13th month study period. All the intravitreal injections were given in the operation room under aseptic precautions using 30G needle by a single ophthalmic surgeon. All patients receiving injections from these vials were clinically followed up till the 15th study month end for clinical evidence of ocular infection or inflammation.

Sterility analysis

Gram staining, KOH mount, as well as blood agar, MacConkey agar, and brain–heart infusion broth were used to assess microbial growth. The Microbiology Laboratory is standardized for ophthalmology specimens, and the media, blood agar and MacConckey agar, were prepared in-house, whereas brain–heart infusion broth was commercial media (HiMedia).

MacConkey agar is used mainly in identifying lactose fermenting and Gram-negative enteric pathogens and for inhibiting Gram-positive organisms. Blood agar is an enriched medium used to isolate fastidious organisms and detect hemolytic activity. Gram staining is one of the differential stains that are used to characterize bacteria in one of two groups: either Gram-positive or Gram-negative bacteria. KOH preparation was used for the detection of fungal elements in clinical specimen. Brain–heart infusion broth was used for the detection of fungal growth.

RESULTS

Twelve sequential Avastin vials with in the expiry period were included in this study. All vials were sent for Gram staining, KOH mount, and culture at the opening of vial and after last vial was used. Hence, the first vial was evaluated at the opening and after 12 months of utilization while the 12th vial was evaluated at the opening and at the end of 1 month utility. All vials were negative for bacterial and fungal growth at both evaluations.

Microbiological evaluation of all the vials preinjection and the 13th study month showed no growth of organisms [Table 1].

DISCUSSION

Bevacizumab (Avastin) is a recombinant monoclonal antibody approved by the FDA for the intravenous treatment of colorectal cancer.[1] Its off-label intravitreal use has shown promise for the treatment of neovascular age-related macular degeneration, diabetic retinopathy, and iris neovascularization.[2,3]

It is a preservative free antiangiogenic drug which is intended for single use and the manufacturer recommends that each vial

Table 1: Microbiological evaluation of vials and clinical outcome

Vial	Number of injections	Microbiological investigations (Gram staining, KOH, and culture)		Patients outcome (presence of ocular infection/ inflammation: Yes/no)
		Preinjection	Postutilization	
1	21	Negative	Negative	No
2	20	Negative	Negative	No
3	9	Negative	Negative	No
4	30	Negative	Negative	No
5	15	Negative	Negative	No
6	16	Negative	Negative	No
7	17	Negative	Negative	No
8	22	Negative	Negative	No
9	20	Negative	Negative	No
10	24	Negative	Negative	No
11	18	Negative	Negative	No
12	20	Negative	Negative	No

KOH – Potassium hydroxide

should be used within 8 h after initial puncturing of the vial. It is available in a vial containing 100 mg in 4 ml solution and one needs only 0.05 ml for intravitreal injection that accounts to 1.25 mg which is commonly used in an ophthalmology practice. Therefore, the contents of the vial can be used on multiple patients and there is significant cost-saving.

A study suggested that if aseptic precautions are followed, the contents of multiple-dose vials stored at 4°C will remain sterile and the Anti-Vascular endothelial growth factor (anti- VEGF) activity of bevacizumab stored at 4°C will remain stable for up to 6 months.[5]

Drawing multiple doses from the same vial immediately before injection has the potential for contamination. Increasing the number of punctures also increases the risk of contamination. This could be due to the rubber septum increasingly wiped by fingers or a dirty gauze, rubber stopper leakage, poor aseptic technique (e.g., entering the vial without alcohol swabbing), injection of air into the vial before removal of the solution, a contaminated needle or syringe used to draw medication, and inappropriate storage durations and temperatures.[6,7]

Our study showed that if proper aseptic precautions are taken such as cleaning the rubber cap with isopropyl alcohol and disinfecting with 10% povidone iodine along with maintaining proper storage conditions and negative preinjection cultures, multiuse vial retains sterility over at least a year's time for its extended use. None of the samples in our study showed microbial contamination during inoculation period or while prolonged refrigerator storage.

Chen *et al*.[5] showed that if proper aseptic precautions are taken while using bevacizumab, the contents of the multidose vial stored at 4°C for 6 months will remain sterile, even with repeated exposure to room temperature during withdrawal.

The authors checked for sterility at 0, 1, 3, and 6 months. In our study, we checked sterility of the contents of multidose vial over a period of 1 year which does not show any microbial growth.

Intravitreal Avastin prepared by compounding pharmacy and injecting in remote areas showed evidence of intraocular infections in various reports.

There was a comment that these events are seemingly artificial[8] and that multiple piercing of vial is unsafe. In this study we demonstrated that multiple piercing of rubber cap and refrigeration at 4°C did not contaminate the vial.

Kamath *et al*.[9] demonstrated that by maintaining proper storage and usage precautions. Bevacizumab vial can be used for multiple times without any increase in an incidence of endophthalmitis. This study was done over a period of 20 months and the vial was used for 1 month which was discarded later regardless of volume.

However, surgeons should be aware of legal issues regarding the use of preservative-free single-use bevacizumab vial for administrating multiple doses.

This is the first study which showed laboratory proven microbiological safety of multidose and multipuncture Avastin vial in correlation with clinical real-life scenario.

None of the used vials which were stored at variable period from 1-12 months showed microbiological contamination. None of the patients who received injections from such vials showed clinical evidence of infection or inflammation on follow-up which consolidates faith in use of multidose Avastin vial for intravitreal injections.

CONCLUSION

In this study, the contents of multiple dose bevacizumab (Avastin) vials remain sterile for a period of 1 year.

Multipuncture, multidose Avastin vial utilization with due aseptic precautions and storage shows reliable microbiological safety both *in vitro* and *in vivo* over a 1 year period.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

A cross sectional study of visual field patterns in advanced primary open-angle glaucoma

ABSTRACT

Objectives: (1) To identify the patterns of visual field defects in patients with primary open-angle glaucoma (POAG) in advanced stage. (2) To identify macular split in patients with POAG in advanced stage. **Materials and Methods:** A cross-sectional study of 180 eyes of 160 patients within a period of 1 year was conducted. All patients with advanced POAG according to the modified Hodapp–Parrish–Anderson criteria were included in the study. A detailed examination including best-corrected visual acuity, color vision, gonioscopy, fundus examination, intraocular pressure measurement, visual field analysis using Humphrey field analyzer, and macular program was done. **Results:** Of the total 180 eyes, 7.2% had 0.8 cup, 67.8% had 0.9 cup, and 25% had glaucomatous optic atrophy. In the 30-2 program, 11.7% eyes had superior arcuate scotoma, 13.9% had inferior arcuate scotoma, 27.8% had double arcuate scotoma, and 46.7% had severely depressed field. In the 10–2 program, 22.8% had normal field, 26.1% had scotomas not involving fixation, and 51.1% had scotomas involving fixation. In the macular program, 63.3% had normal result, 18.3% had macular threat, and 18.3% had macular split. **Conclusions:** The most common field defect in the 30–2 program was severely depressed field. The most common defect in the 10–2 program was scotomas involving fixation. The macular program was normal in a majority of patients.

Keywords: Field defects, macular split, primary open-angle glaucoma

INTRODUCTION

Primary open-angle glaucoma (POAG) is an adult onset, bilateral, symmetrical disease. It is one of the leading causes of blindness worldwide. The field changes in POAG are initially seen in the Bjerrum's area (10°–25° around fixation) and gradually increase according to the optic disc changes. Field defects in advanced glaucoma are diagnosed with the help of the Hodapp–Parrish–Anderson criteria [Table 1].[1]

Macular split is a field defect observed in the advanced stage. Split macular fixation is defined as one of the four points abutting fixation on the macular program having a sensitivity of a single digit (<10, normal threshold being in the 30s) with an adjacent point on the same side of fixation in another quadrant also being <10 [Figure 1].

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Studies published so far have attempted to compare various methods to assess the progression of field defects.

This study aims to analyze the different patterns of visual field defects in advanced POAG and also to document the occurrence of macular split in these cases.

MATERIALS AND METHODS

Study design

Cross-sectional study.

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Table 1: Hodapp-Parish-Anderson criteria

Early glaucomatous loss
MD <-6 dB
<18 points depressed below the 5% probability level and less than 10 points below the $p<1\%$ level
No point in the central 5 degrees with sensitivity of <15
Moderate glaucomatous loss
MD <-12 dB
<37 points depressed below the 5% probability level and <20 points below the $p<1\%$ level
No absolute deficit (0 dB) in the central 5 degrees
Only one hemifield with sensitivity of <15 dB in the central 5 degrees
Advanced glaucomatous loss
MD >-12 dB
More than 37 points depressed below the 5% probability level or more than 20 points below the $p<1\%$ level
Absolute deficit (0 dB) in the central 5 degrees
Sensitivity of <15 dB in the central 5 degrees in both hemifields

MD – Mean deviation

Study setting

Department of ophthalmology of a tertiary care hospital in Kerala.

Study population

Patients attending the glaucoma clinic of department of ophthalmology and diagnosed as having advanced POAG.

Inclusion criteria

Patients with advanced POAG according to the modified Hodapp–Parrish–Anderson criteria.

Exclusion criteria

a. Early stages of POAG
b. Secondary glaucoma
c. Closed-angle glaucoma.

Sample size calculation

For the significance level, $\alpha = 5\%$

Sample size, $n = \frac{Z^2{}_{\alpha} \times pq}{d^2}$

where P = prevalence = 38% [84]

$q = 1 - p$

d = precision = 0.2 p

hence $n = \frac{1.96^2.96e}{0.076^2} = 156.6$

Sample size = 160

Study Period

One year.

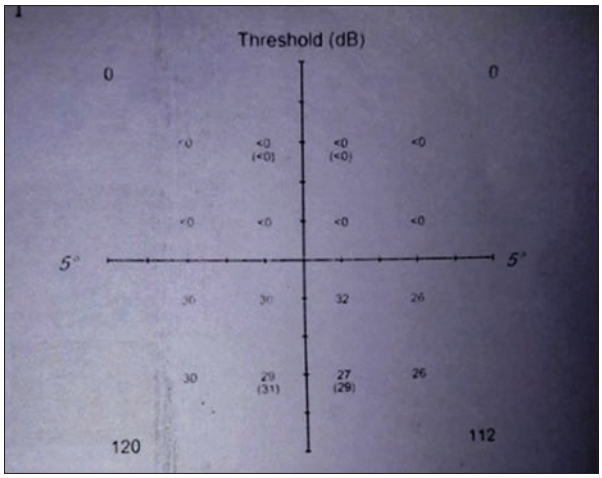


Figure 1: Macular split

Methodology

Ours was a hospital-based cross-sectional study. 180 eyes of 160 patients diagnosed as having advanced POAG were selected based on the inclusion and exclusion criteria. These patients are on follow-up at the glaucoma clinic at our institution. Informed consent was obtained from all patients and details of the study were explained. Approval was obtained from the institutional ethics committee and the institutional review board.

Patient biodata and sociodemographic details were recorded. A brief medical and ophthalmic history was taken and patients were asked to fill up the study pro forma. Patients were then clinically evaluated as follows:

a. Visual acuity using Snellen's or E chart
b. Color vision using Ishihara chart
c. Pupils were assessed. Swinging flashlight test was done to look for relative afferent pupillary defect
d. Slit-lamp examination using Haag–Streit slit lamp
e. Intraocular pressure by applanation tonometry
f. Direct ophthalmoscopy using a Keeler direct ophthalmoscope
g. Indirect ophthalmoscopy
h. Indirect gonioscopy using Goldmann single-mirror gonioprism
i. Slit-lamp biomicroscopy using Volk 90D lens
j. Visual field tested on Humphrey Field Analyzer II (SITA standard) using 30–2, 10–2, and macular programs.

Patients were selected till sample size was attained.

Study variables

a. Age
b. Sex
c. Duration
d. Family history

e. Vision
f. Color Vision
g. Pupil
h. Cup–disc ratio (CDR)
i. Intraocular pressure
j. 30-2
k. 10-2
a. Macular program

Patient data were recorded on a pro forma, coded, and entered into a Microsoft Excel spreadsheet. Statistical Package for the Social Sciences (SPSS Version 20) (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) was used for statistical analysis. Variables were represented using frequency and percentage analysis.

RESULTS

This study included 180 eyes of 160 patients. The following were our observations:

1. Age: The age-wise distribution of patients is shown in Table 2. Majority of patients were above the age of 55 years
2. Sex: Males formed a major share of the patients in this study
3. Family history: Only 13% of the subjects had a positive family history
4. Vision: Most of our patients had vision visual acuity more than 6/12 with maximum number in 6/9 category as shown in Table 3
5. Color vision: 62.8% of eyes had retained normal color vision whereas 37.2% of eyes had defective color vision
6. Pupils: A normal brisk pupillary reaction was observed in a majority of patients and only 26.7% of our patients with advanced glaucoma had a relative afferent pupillary defect
7. CDR: The distribution of cup to disc ratio is shown in Table 4 and Figure 2
8. Intraocular pressure was <12 in 93 out of 180 eyes
9. 30-2: The results showed that most patients with advanced glaucoma had a severely depressed field [Table 5 and Figure 3]
10. 10–2: 51% of the eyes had scotomas involving fixation in the 10–2 program. [Table 6 and Figure 4]
11. Macular program: A normal study was obtained in 63% of the eyes studied and only a minority had a macular split [Table 7 and Figure 5]
12. The comparative data between the CDR and the field patterns are summarized in Tables 8-10.

Table 2: Distribution of age

Age category (years)	Frequency (%)
25-34	9 (5.0)
35-44	2 (1.1)
45-54	25 (13.9)
55-64	52 (28.9)
65-74	67 (37.2)
75 and above	25 (13.9)
Total	180 (100.0)

CDR – Cup-disc ratio

Table 3: Distribution of vision

Vision	Frequency (%)
6/6	21 (11.7)
6/9	45 (25.0)
6/12	35 (19.4)
6/18	31 (17.2)
6/24	15 (8.3)
6/36	7 (3.9)
6/60	8 (4.4)
<6/60	18 (10.0)
Total	180 (100.0)

Table 4: Distribution of cup-disc ratio

CDR	Frequency (%)
0.8	13 (7.2)
0.9	122 (67.8)
Advanced cupping	45 (25.0)

CDR – Cup-disc ratio

Table 5: Distribution of results of 30-2 program

Field defect	Frequency (%)
Superior arcuate scotoma	21 (11.7)
Inferior arcuate scotoma	25 (13.9)
Double arcuate scotoma	50 (27.8)
Severely depressed	84 (46.7)
Total	180 (100.0)

Table 6: Distribution of results of 10-2 program

Field defect	Frequency (%)
WNL	41 (22.8)
Scotomas not involving fixation	47 (26.1)
Scotomas involving fixation	92 (51.1)
Total	180 (100.0)

DISCUSSION

In this study, we have analyzed the various visual field patterns in advanced POAG. We analyzed 180 eyes of 160 patients who satisfied the inclusion criteria for advanced POAG. The progression of field changes in chronic open-angle glaucoma has already been described. Different patterns of visual defects are seen depending on the optic disc damage, though the field defects cannot be always be predicted from the appearance of the optic disc. Here, we have examined the visual fields and the clinical profile of patients with advanced POAG.

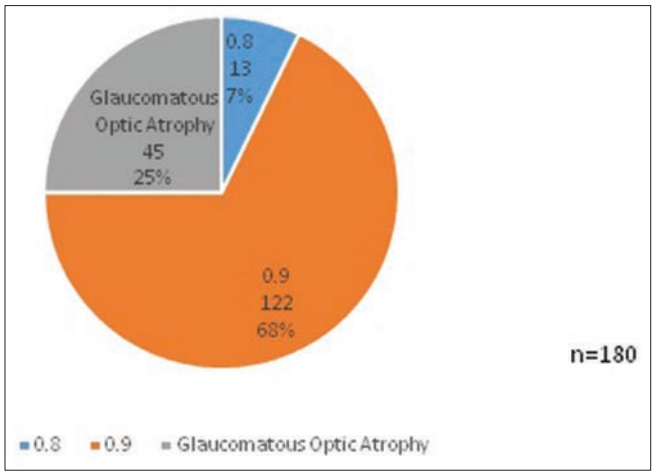


Figure 2: Distribution of Cup–disc ratio

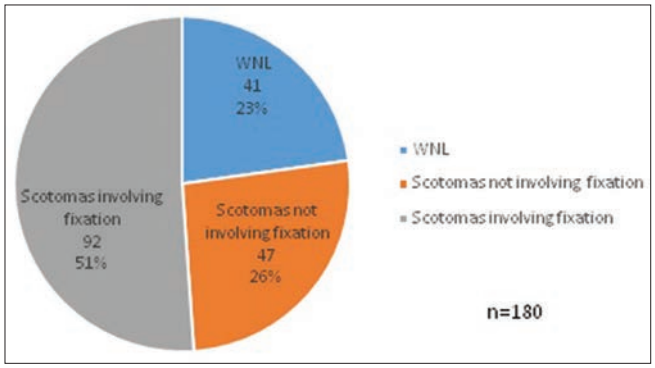


Figure 4: Distribution of results of 10–2 program

Table 7: Distribution of results of macular program

Field defect	Frequency (%)
WNL	114 (63.3)
Macular threat	33 (18.3)
Macular split	33 (18.3)
Total	180 (100.0)

Age: Most patients in our study were above the age of 55 years. The minimum age was 28 and the maximum age was 85 years. A study conducted by Cedrone *et al.* states that one-third of the population between the age group of 40–75 years suffered from open-angle glaucoma.[2] Similar results were obtained in a study conducted by Kroese *et al*.[3]

Sex: Males formed a majority of patients in our study. Around 74% were male and 26% were female. In a study conducted by Rudnicka *et al*., it was found out that men are more likely to develop open-angle glaucoma than females[4]

Family history: Though family history is a very significant risk factor for development of POAG, it was positive in only 13.3% of eyes with advanced disease

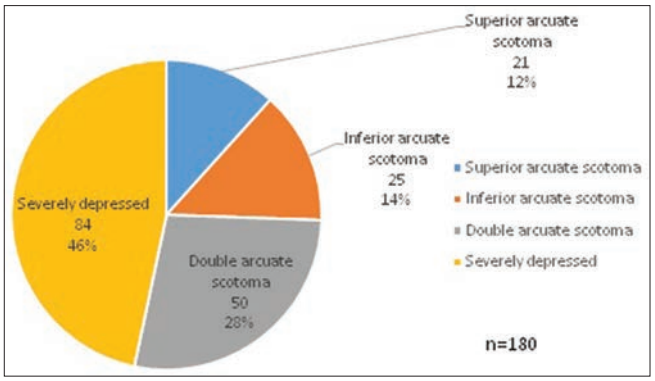


Figure 3: Distribution of results of 30–2 program

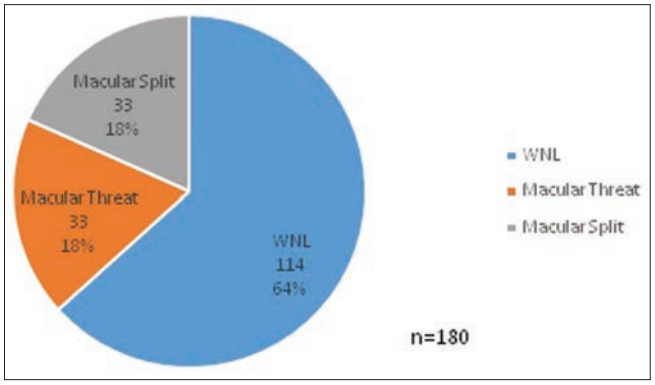


Figure 5: Distribution of results of macular program

Vision: Most of our patients had vision visual acuity more than 6/12 with maximum number in 6/9 category. Visual acuity was largely preserved in patients with advanced disease even though their visual fields were constricted. This is due to the fact that the retinal ganglion cells in the papillomacular area are preserved till the end. Vision is affected when these are also damaged as in 18 eyes in our study where the vision was less than 6/60. This has been reported in a study by Asaoka[5]

Color vision: 62.8% of eyes had retained normal color vision whereas 37.2% of eyes had defective color vision. It was mainly those eyes with glaucomatous optic atrophy that demonstrated defective color vision. A study conducted by Niwa *et al.* confirms that color vision especially blue–green defects are associated with glaucoma[6]

Pupils: A relative afferent papillary defect was seen in 26.7% and they were sluggish in 5% of eyes. 68.3% of eyes had a normally reacting pupil. The presence of a relative afferent papillary defect denotes asymmetric damage to the optic nerve and is commonly seen in the late stages of glaucoma.[7] A study conducted by Page *et al.* opined that quantitative analysis of RAPD by neutral density filter correlates better with visual field loss. In our study, only swinging torchlight examination was done

Table 8: Results of 30-2 versus cup-disc ratio

CDR	Superior arcuate scotoma	Inferior arcuate scotoma	Double arcuate scotoma	Severely depressed field	Total
0.8					
Number of eyes	3	4	4	2	13
Percentage	23.1	30.8	30.8	15.4	100
0.9					
Number of eyes	18	21	41	42	122
Percentage	14.8	17.2	33.6	34.4	100
Advanced cupping					
Number of eyes	0	0	5	40	45
Percentage	0	0	11.1	88.9	100
Total					
Number of eyes	21	25	50	84	180
Percentage	11.7	13.9	27.8	46.7	100

CDR – Cup-disc ratio

Table 9: Results of 10-2 versus cup-disc ratio

CDR	WNL	Scotomas not involving fixation	Scotomas involving fixation	Total
0.8				
Number of eyes	4	2	7	13
Percentage	30.8	15.4	53.8	100
0.9				
Number of eyes	35	39	48	122
Percentage	28.7	32	39.3	100
Advanced cupping				
Number of eyes	2	6	37	45
Percentage	4.4	13.3	82.2	100
Total				
Number of eyes	41	47	92	180
Percentage	22.8	26.1	51.1	100

CDR – Cup-disc ratio

Table 10: Results of macular program versus cup-disc ratio

CDR	WNL	Macular threat	Macular split	Total
0.8				
Number of eyes	11	1	1	13
Percentage	84.6	7.7	7.7	100
0.9				
Number of eyes	92	19	11	122
Percentage	75.4	15.6	9	100
Advanced cupping				
Number of eyes	11	13	21	45
Percentage	24.4	28.9	46.7	100
Total				
Number of eyes	114	33	33	180
Percentage	63.3	18.3	18.3	100

CDR – Cup-disc ratio

Perimetry and cup–disc ratio.

a. 30-2: In this study, 46% of eyes had severely depressed fields followed by double arcuate scotoma. Thirty-four percent of eyes with severely depressed fields had a cup–disc ratio of 0.9 and 89% of eyes had glaucomatous optic atrophy. 13.9% of eyes had inferior arcuate scotoma and 11.7% had superior arcuate scotoma
b. 10–2: In our study, 51.1% of eyes had scotomas involving fixation whereas 22.8% had a normal field in 10–2 program. Most eyes with glaucomatous optic neuropathy had scotomas involving fixation (82.2% of eyes). In the late stages, the central vision gets affected and this is better picked up with a 10–2 field analysis.[8] Even in very advanced cupping, 4.4% had a normal field. This is probably due to remaining unaffected ganglion cells in the macula
c. Macular program: Around 63.3% of eyes had a normal macular program. 24.4% of eyes with advanced cupping had a normal program in spite of having severely depressed fields on 30–2 program. Only 18% of total sample had macular split. This could be explained by the fact that the macular program tests only the central 16 points around 5 degrees of fixation which would be the last to be lost. Furthermore, this program would be less tiring for the patient and less time-consuming and hence the patient's response would be more accurate

CONCLUSIONS

- The most common field defect in 30–2 program was a severely depressed field

- The maximum result in 10–2 program was scotomas involving fixation
- Macular program was normal in a majority of patients.

Limitations of the Study

Our sample size was limited as it was a time bound study. A larger sample size over a longer period of time would be more beneficial. Furthermore, color vision was analyzed using the Ishihara chart. A detailed evaluation of the type of color vision affected in advanced glaucoma would be a better analysis. In patients with bilaterally defective color vision, congenital color blindness was not ruled out. Relative afferent pupillary defects should be quantified with a neutral density filter. This could not be done in our study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Digital eye strain among undergraduate medical students during the COVID-19 pandemic: A cross-sectional survey

ABSTRACT

Background and Objective of the Study: The COVID-19 pandemic has increased the use of online platforms for education. This may lead to digital eye strain (DES) in the student community. The objective of this study was to assess the pattern of digital device use, the prevalence of DES symptoms and assess the awareness of DES among undergraduate medical students. **Materials and Methods:** This was a cross-sectional study and was conducted among undergraduate medical students of a medical college in Kerala using a structured, self-administered online questionnaire. **Results:** Two-hundred and twenty-seven students responded to this questionnaire. Of these respondents, 90.3% (205 students) reported experiencing the ocular and extra-ocular symptoms of DES. Neck pain, headache, and watering of eyes were the most frequent symptoms. Continuous use of devices without breaks, the predominant activity on devices, the presence of refractive errors, and inappropriate control of glare on digital devices had a statistically significant association with DES. Although 79.4% of students were aware that using digital devices can cause eye strain, <20% were aware of the ideal distance for viewing digital screens and the 20-20-20 rule of taking breaks in-between screen time. **Conclusion:** Undergraduate medical students reported a high prevalence of DES during the COVID-19 college shutdown. Lack of timely breaks and inappropriate control of glare from monitors were associated with DES symptoms. Only a few students were aware of the ergonomic measures to be adopted during device use. Educating undergraduate medical students about DES is essential to curb this rising problem.

Keywords: Asthenopia, computer vision syndrome, digital eye strain, gadget use

INTRODUCTION

The COVID-19 pandemic has created new challenges in medical education worldwide.[1] Online lectures and clinical scenarios have replaced conventional teaching in the clinics and wards. Technology has enabled us to communicate and disseminate information, even during this challenging period. However, we must be aware of the ophthalmologic and psychosocial problems that may occur because of the unmitigated usage of digital devices.

Digital eye strain (DES) refers to the ocular and extra-ocular symptoms because of digital device use. The ocular symptoms of DES include asthenopic symptoms such as eyestrain, headache, tired eyes; vision-related symptoms such as blurred vision and double vision; ocular-surface-related symptoms such as watery eyes, burning sensation of the eyes, and redness of eyes. The extra-ocular symptoms include neck pain, back pain, and upper extremity pain.[2]

Utilizing good ergonomic practices can mitigate the symptoms of DES. These include using adequate illumination, adopting appropriate posture, taking frequent breaks and adjusting screen brightness, resolution, and font size.[3]

This study aims to survey the undergraduate medical students of a government medical college in North Kerala to assess the

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pattern of digital device use, the prevalence of the symptoms of digital eye-strain, and the awareness regarding DES.

Objectives

1. To evaluate the pattern of digital device usage among undergraduate medical students
2. To estimate the prevalence of symptoms of DES among undergraduate medical students
3. To assess the awareness among undergraduate medical students regarding DES and the practices to prevent it.

MATERIALS AND METHODS

Study design, study period, and setting

This was a cross-sectional questionnaire-based study done at a tertiary care teaching institute in Kerala. It was conducted from June to September 2020. This center has 1000 undergraduate medical students.

Sample size determination

The sample size was determined with the following assumptions: margin of error 5%, the proportion of DES 89.9%,[4] 95% confidence interval (CI), and population size of 1000 to come up with a sample size of 127 respondents.

Data collection method

A self-administered questionnaire was prepared based on the symptoms of DES identified in the current literature.[5,6] An initial pilot on 5% of the sample was conducted. Based on posttest feedback, any leading or confusing questions were appropriately rephrased. It was then sent to the students through E-mail and circulated within student groups.

The questionnaire had three parts:

1. The first part of the questionnaire had 13 items. The initial three items were on the socio-demographic characteristics. The next 10 items were on the pattern of digital device usage, including the device most frequently used, hours spent on technological devices per day, how frequently breaks are taken during electronic use, the eye-to-screen distance and the position in which devices are used
2. The second part of the survey had nine questions. These were on the validated symptoms of DES (headache, dry eyes, burning eye sensation, eye redness, blurred vision, neck, and shoulder pain). The symptoms were graded as mild (transient symptoms for a few minutes to an hour), moderate (continues for hours and subsides after rest), or severe (needs medications)
3. The third part of the questionnaire contained 11 questions. These were regarding the awareness of DES and pattern of device use among the undergraduate medical students.

The survey questionnaire is given as Supplementary Material 1.

Data processing and analysis

The data were analyzed using SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Ill., USA). The descriptive data were presented as frequencies and percentages. Pearson's Chi-square test and odds ratio were used to measure the association between categorical study and outcome variables. For statistical significance and precision, we used a $P < 0.05$ and a 95% CI.

Ethical considerations

The ethical clearance was taken from the Institutional Review Board of the institution. Informed consent was sought from all the participants after describing the purpose of the study. All participants were informed of their right to withdraw at any time, without any obligation toward the study team. No incentives were offered to the study participants, and confidentiality of the data was maintained.

RESULTS

Demographics and digital device use pattern

Two-hundred and twenty-seven undergraduate medical students responded to the questionnaire. The age of the students ranged from 18 to 26 years, with a mean age of 21 years. Of the respondents, 134 were female (59%) and 93 males (41%). The smartphone was the most regularly used device by 216 students (95%). Six students reported spending the most time with tablets and five with laptops.

One hundred and sixty students (70%) reported spending over 6 h with digital devices, 50 (22%) spent between 4 and 6 h, and 17 (7%) spent between 2 and 4 h. Ninety-five students reported browsing social media to be their most frequent activity, 60 students (26%) used most of their screen time for watching movies or television shows, 36 students (15%) spend the most time on their devices for academic purposes. For 22 students (10%) gaming was the chief activity, and 14 students (6%) spent maximum time on gadgets for recreational reading.

The time spent by the students on technological devices for their academics varied from <2 h in 95 students (42%), 2–4 h in 85 students (37%) to over 4 h in 47 students (21%). The preferred device for studying was the smartphone in 57% of the students. The most common posture adopted by the students for device use was sitting upright with a bent back (87 students), followed by the supine position (76 students), upright position with straight back in 47 students and the least used was the prone position (17 students). One hundred and fifty-five students (68%)

used their devices at nighttime with the lights switched off, while 57 students used multiple devices at the same time. One-hundred and forty-two students (62.5%) reported more than a four-hour increase in screen time after the COVID-19 college shutdown [Figure 1].

Digital eye strain symptoms

The symptoms of DES were present in 205 of the 227 students who had participated in this study. Thus, the self-reported prevalence of DES among undergraduate medical students was 90.3% (95% CI-86.3, 94.3). The most common symptoms were neck pain (128 students), headache (125 students), and watering of eyes (97 students). Seventy-eight students had a backache, 72 had itchy eyes, 65 students had burning sensation of eyes, while 48 experienced redness of the eyes.

Digital exposure and digital eye strain

All the symptoms of DES investigated in this study showed a proportional relationship with the continuous use of electronic gadgets for over ½ h. However, only blurred vision, burning sensation of eyes and back pain reached levels of statistical significance. Further, using gadgets for over 4 h/day had greater odds of developing asthenopic and musculoskeletal symptoms, but this was not statistically significant [Table 1]. Regarding primary activity on digital devices, social media browsing (95.8%) and gaming (95.5%) showed the highest prevalence of DES symptoms. This was statistically significant ($\chi^2 = 11.33$, df = 4, $P = 0.047$).

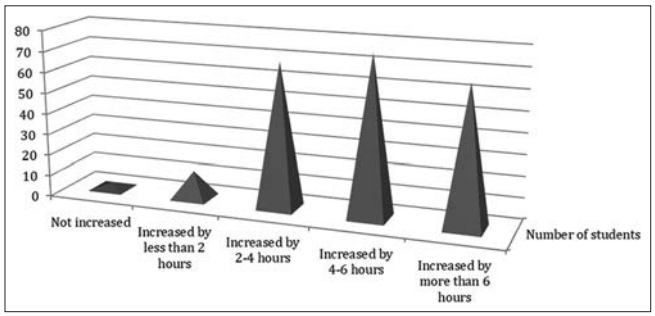


Figure 1: Effect of the COVID-19 induced college shutdown on electronic device use among medical students

Refractive error

Blurred vision after using electronic devices was seen more frequently in those with refractive errors (35.4%) than those without refractive errors (18%). This was statistically significant (odds ratio [OR]-2.6, 95% CI-1.42–4.80, $P = 0.03$). Among those with refractive error, we found a higher prevalence of blurred vision after gadget use those with myopia and astigmatism. This was also statistically significant ($\chi^2 = 13.39$, $P = 0.01$).

Digital eye strain and ergonomic factors

Of the 228 students, 128 students (56.4%) developed neck pain, 78 students had back pain (34.4%), and 53 students (23.35%) developed wrist or finger stiffness after digital device use. We analyzed the prevalence of musculoskeletal symptoms among the students with regard to the predominant posture adopted by them. Neck pain was most in those who primarily used devices in prone position and back pain in those who sat upright with a bent back.

The prevalence of DES symptoms among those who kept their smartphones less than arm's length away was 91.9%, those who kept a distance of an arms-length-88.2% and those who kept devices more than arm's length away was 85.7%. This was not statistically significant. There was also no statistically significant correlation between DES symptoms and the device primarily used, using electronic displays in the dark and using multiple devices simultaneously.

Awareness regarding digital eye strain

Out of the 228 medical students, 181 (79.4%) were aware that using digital devices can cause DES. Of these, 102 (44.9%) knew about the symptoms of DES. Eighty-six students (37.7%)

Table 1: Symptoms of digital eye strain and digital exposure time

	Daily use of devices >4 h (%)	OR with (CI)	Daily use of devices <4 h (%)	Pearson's χ^2	*P*	Continuous use of devices without break >30 min (%)	OR with (CI)	Continuous use of devices <30 min (%)	Pearson's χ^2	*P*
Headache	56.2	1.83 (0.67-5.00)	41.2	1.43	0.23	56.8	1.37 (0.73-2.56)	49	0.97	0.32
Blurred vision	27.1	2.79 (0.62-12.6)	11.8	1.93	0.16	30.7	4.07 (1.53-7.74)	9.8	8.96	0.003
Watering	42.9	1.07 (0.39-2.92)	41.2	0.018	0.89	44.9	1.67 (0.87-3.20)	33.3	2.37	0.12
Redness	23.5	0.86 (0.27-2.77)	21	0.063	0.80	23.3	1.9 (0.79-4.56)	13.7	2.17	0.14
Burning	28.6	0.96 (0.32-2.84)	29.4	0.005	0.94	33	3.09 (1.31-7.28)	13.7	7.16	0.007
Neck pain	56.7	1.16 (0.43-3.13)	52.9	0.09	0.77	58.5	1.47 (0.79-2.74)	49	1.45	0.23
Back pain	23.8	1.28 (0.43-3.77)	17.6	0.2	0.56	38.1	2.23 (1.07-4.65)	21.6	4.78	0.029

OR: Odds ratio, CI: Confidence interval

had heard about the harmful effects of blue light emitted from electronic visual displays. Only 34 students (14.9%) knew about the ideal working distance for the use of electronic devices and 26 students (11.4%) had heard of the 20-20-20 rule. One hundred and sixty-five students (72.6%) used applications to control glare. The odds of developing burning sensation and itching were lower among the group utilizing applications for reducing glare (OR = 0.53, 95% CI-0.28–0.97, $P = 0.04$).

More female students had heard the term DES (62.8%) and this was statistically significant ($\chi^2 = 5.05$, $P = 0.02$). However, awareness about the symptoms of DES did not vary with gender. The awareness of the term DES, its symptoms and the awareness of the proper working distance of various devices and the 20-20-20 rule varied with the year of study [Table 2].

DISCUSSION

This study explored the pattern of digital device use, the prevalence of DES, symptoms of DES and the knowledge, attitude, and practices regarding DES among undergraduate medical students during the COVID-19 college shutdown.

The prevalence of DES among the students was 89.9%. This is close to the other similar studies in the literature [Table 3]. The most frequent symptoms encountered in this study was neck pain and headache. Sanodiya *et al*., Abudawood *et al*., Logaraj *et al*. and Reddy *et al*. found neck pain to be most common, while Al Tawil *et al*. and Mowatt *et al*. reported headache as the most common symptom.[4,7,8,10,11,13]

Asthenopic symptoms

Headaches and tired eyes are a significant cause of interruption to the work of the students.[12] In our study, 21.6% of students had moderate-to-severe headache following digital device use. The reason for asthenopic symptoms following gadget use may be because of (1) changes in the accommodation (increased lag and decreased amplitude) and (2) changes in the vergence (receding of near point of convergence and decreased positive and negative fusional vergence.[14]

Refractive error and digital eye strain

In this study, there was a statistically significant association between refractive error and blurred vision after prolonged gadget use. Bhanderi *et al*. and Nakaishi and Yamada had noted more asthenopic symptoms after gadget use in those with corrected refractive errors.[15,16] We found that myopia and astigmatism had a higher degree of eye strain. Schellini *et al*. and Hashemi *et al*. have reported higher gadget-use-related asthenopia in those with astigmatism and myopia.[17,18] This may be because of the increased accommodative effort in placing the circle of least confusion on the retina in astigmatism. Since the number of hypermetropes in this study was low compared to myopes, larger studies are needed to establish whether myopes experience more DES symptoms.

Dry eye symptoms

We found statistically significant higher odds of developing burning sensation of the eyes on using devices continuously for over 30 min without breaks. Several studies have reported dry eye symptoms after continuous gadget use. The reason for this may be the reduced blink rate.[19,20] Again, the decreased blink rate may be due to involuntary eyelid squinting, which helps in improving visual acuity and reducing retinal illumination.[21,22] Another reason for dry eyes may be the higher percentage of incomplete blinks.[23] This study also found a significantly lower prevalence of burning sensation among those who used applications to control glare on their screens ($P = 0.04$). This highlights that even simple measures such as adjusting the display brightness can help reduce DES.

Musculoskeletal symptoms

A survey by Hupert *et al*. in college students reported a 42% prevalence of computer-associated upper extremity musculoskeletal symptoms.[24] Our respondents also reported a high prevalence of neck, back and wrist pain or stiffness following electronic device use. These symptoms were highest in those who used devices in the prone position and on using devices in an upright position with a bend back. As opined by Toh *et al*., the use of touch-screen on mobiles and their portability leads to unconventional postures and greater musculoskeletal stress, even more than conventional

Table 2: Level of awareness among undergraduate medical students classified according to the year of study

	First years ($n=48$), *n* (%)	Second years ($n=50$), *n* (%)	Third years ($n=41$), *n* (%)	Fourth years ($n=38$), *n* (%)	Final years ($n=50$), *n* (%)	χ^2	*P*
Heard about DES	28 (58.3)	38 (76)	33 (80.5	34 (89.5)	47 (94)	22.2	<0.0005
Aware of symptoms of DES	8 (16.7)	17 (34)	23 (60.5	23 (56.1)	31 (62)	29.6	<0.0005
Aware of 20-20-20 rule	5 (10.4)	1 (2)	5 (12.2)	5 (13.2)	10 (20)	8.19	0.085
Aware of working distance	8 (16.7)	6 (12)	9 (22)	6 (15.8)	5 (10)	3.01	0.556

DES: Digital eye strain

visual display terminal use. This manifests as neck, shoulder, and wrist and finger stiffness.[25]

Digital exposure and eye strain

Many studies have reported associations between both total hours of digital exposure and continuous digital usage [Table 4]. In the present study, the use of devices for over 4 h a day had higher odds of developing DES symptoms; however, this was not statistically significant. The symptoms of blurred vision, burning sensation and back pain had a statistically significant relationship with continuous device use for over 30 min without breaks. We had also assessed the awareness of the 20-20-20 rule (every 20 min spent looking at a screen, look away at an object 20 feet away for 20 s). Among the medical students surveyed in this study, only 11% were aware of this rule, suggesting a lack of knowledge among the students regarding the appropriate timing and duration of the breaks to be taken during computer use.

Other factors contributing to digital eye strain

In this study, browsing social media and gaming had the highest prevalence of DES symptoms. A study conducted

Table 3: Prevalence of digital eye strain and its symptoms in literature

	Study population	Year of study	Prevalence of DES (%)	Headache (%)	Redness (%)	Burning sensation (%)	Watering (%)	Blurred vision (%)	Neck pain (%)	Back pain (%)
Present study	227 undergraduate medical students	2020	89.9	56	21	29	43	26	57	35
Sanodiya *et al.*[4]	200 college student in Indore	2019	89.5	89	—	—	80	77	79	80.5
Abudawood *et al.*[7]	651 undergraduate medical students in Jeddah	2019	95	30.1	15.1	15	20.6	11.4	—	
Al Tawil *et al.*[8]	775 undergraduate university students in Saudi Arabia	2018	—	66.5	40.8	58.3	—	44.6	82.2	—
Iqbal *et al.*[9]	100 medical students Egypt	2017	86	26	15	—	—	31	24	—
Mowatt *et al.*[10]	409 undergraduate medical students in West Indies	2017	—	67	—	61.9	—	51.6	75.1	—
Logaraj *et al.*[11]	201 medical students in Chennai	2014	78.6	43.3	13.9	32.3	—	16.4	61	—
Shantakumari *et al.*[12]	500 students in UAE	2014	—	53.3	—	54.8	—	24.8	—	—
Reddy *et al.*[13]	795 university students in Malaysia	2013	89.9	19.7	2.4	10.2	4.3	10.2	9.9	6.8

DES: Digital eye strain

Table 4: Digital exposure and eyestrain

	Year of study	Study population	Association between daily device use and DES symptoms	Association between continuous device use without breaks and asthenopic symptoms
Present study	2020	227 undergraduate medical students	Those who used devices for more than 4 h daily had higher odds of having asthenopic and musculoskeletal symptoms	Odds of developing asthenopic, ocular surface and musculoskeletal symptoms were higher among those who used devices for more than 30 min without breaks
Lee *et al.*[26]	2019	50 healthy college students	—	Continuous computer gaming for 4 h resulted in musculoskeletal, asthenopic and ocular surface symptoms
Agarwal *et al.*[27]	2013	150 computer users between 18 and 39 years	All ocular complaints were more in those using devices for more than 6 h	There was a statistically significant increased prevalence of eyestrain among those who did not take breaks at least once every hour during computer use
Rahman and Sanip[28]	2011	Cross-sectional survey of university staff	Those with more than 5 h of computer usage were significantly having a higher odds of computer vision syndrome	Not taking breaks while on continuous 1-h computer work was a predictor of computer vision syndrome
Moon *et al.*[29]	2016	916 school children	Dry eye disease was more among children with a higher mean duration of device use	-

DES: Digital eye strain

by Masthi and Manasa among college students in Bengaluru found an increased eye strain and neck pain among social media users.[30] Studies have also reported a higher occurrence of asthenopic, dry eye, and musculoskeletal symptoms among gamers.[26] The high prevalence of DES symptoms in both these activities may be because of their addictive nature, leading to continuous use.

Using multiple devices at the same time is called dual or triple screening. Studies regarding the impact of dual screening on accommodation and convergence are scarce.[14] There is also a scarcity of data regarding the use of devices in the dark and DES symptoms. In this study, there was no association between dual screening, use of devices in the dark, and symptoms of DES.

Awareness of digital eye strain among undergraduate medical students

In this study, 79% of the students had heard of DES, though only 45% aware of the symptoms and about 11%–14% were aware of the proper ergonomic measures to be taken while using digital devices. Although the awareness regarding DES increased with the year of study, knowledge of the preventive measures was low, even among final-year medical students. These gaps in the knowledge maybe because of the low emphasis in the undergraduate ophthalmology curriculum on the management of DES.[31] Hence, this study also highlights the need for greater awareness among the medical community regarding the symptoms of DES and the ergonomic measures that need to be adopted while using digital devices.

CONCLUSION

A significant number of undergraduate medical students suffer from symptoms of DES. Watering of eyes, headache, and neck pain were the most commonly encountered symptoms. Proper ergonomic measures are of paramount importance in preventing DES. However, only a few students were aware of these measures. Both the general ophthalmologist and ophthalmology teachers of medical schools should prioritize awareness activities regarding DES. This is especially important during this global COVID pandemic, where electronic device use has escalated.

Limitations

This study was a self-administered, anonymous, opt-in survey. As the ophthalmic examination was not performed, the accuracy of the information submitted could not be verified. Furthermore, this study was confined to a single institution and so the discussion and interpretation may not be applicable to the general population of medical students.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL 1

Digital eye strain survey

1. How old are you?
2. What is your gender?
   a. Male
   b. Female.
3. Which year of medical education are you in?
   a. First year
   b. Second year
   c. Third year
   d. Fourth year
   e. Final year
4. Which digital device do you use the most?
   a. Smartphone
   b. Tablet
   c. Laptop
   d. Desktop computer
   e. Television
5. Which is your second most commonly used device?
   a. Smartphone
   b. Tablet
   c. Laptop
   d. Desktop computer
   e. Television
6. How much time per day do you spend on digital devices?
   a. Less than 2 h
   b. 2–4 h
   c. 4–6 h
   d. More than 6 h
7. On what activity do you spend the maximum time on your digital devices?
   a. Watching movies
   b. Studying
   c. Recreational reading
   d. Social media
   e. Playing games.
8. How much time do you spend on your favorite activity on your digital device?
   a. Less than 2 h
   b. 2–4 h
   c. 4–6 h
   d. More than 6 h
9. Which is your preferred device for studying?
   a. Smartphone
   b. Tablet
   c. Laptop
   d. Desktop computer
10. How many hours per day do you currently spend on digital devices for your academic activities?
    a. Less than 2 h
    b. 2–4 h
    c. More than 4 h.
11. Which is your most commonly used posture while using your smartphone?
    a. Upright with bend back
    b. Upright with straight back
    c. Lying down in supine position
    d. Lying down in prone position
12. At what working distance do you usually use your smartphone?
    a. Less than arm's length away
    b. About an arm's length away
    c. More than arm's length away
13. Approximately how long do you usually use any digital device at a stretch?
    a. 30 min
    b. 1 h
    c. 2 h
    d. More than 2 h
14. Do you experience any headache after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
15. Are you experiencing any blurred vision after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
16. Do you experience any watering of eyes after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires use of medications for relief
17. Do you experience any redness of eyes after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
18. Do you experience any burning sensation of eyes after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours

c. Moderate - persists for hours and is relieved by rest or sleep
d. Severe - requires use of medications for relief

19. Do you experience any itching of eyes after prolonged use of digital devices?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
20. Do you experience any neck pain after prolonged digital device use?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
21. Do you experience any backache after prolonged digital device use?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires use of medications for relief
22. Do you experience any wrist pain after prolonged smartphone use?
    a. No
    b. Mild- persists for a few minutes to few hours
    c. Moderate - persists for hours and is relieved by rest or sleep
    d. Severe - requires the use of medications for relief
23. Do you use your device at night before sleeping with the lights switched off?
    a. Yes
    b. No
24. Do you use your multiple devices at the same time?
    a. Yes
    b. No
25. Do you have a refractive error which requires you to wear spectacles or contact lenses?
    a. Yes
    b. No
26. If yes, what refractive error do you have?
    a. Simple myopia
    b. Simple Hypermetropia
    c. Astigmatism
    d. I don't know
27. Have you heard about digital eye strain?
    a. Yes
    b. No
28. Are you aware of the symptoms of digital eye strain?
    a. Yes
    b. No
29. Do you know about the effects of blue light emitted from digital devices?
    a. Yes
    b. No
30. Have you heard about the 20-20-20 rule?
    a. Yes
    b. No
31. Do you know the ideal working distances for each digital device?
    a. Yes
    b. No
32. Do you use applications to control the brightness of your display screen?
    a. Yes
    b. No
33. By how much has your digital device use increased during this COVID Lockdown period?
    a. Increased by < 2 h
    b. Increased by 2–4 h
    c. Increased by 4–6 h
    d. Increased by more than 6 h
    e. Not increased.

Original Article

Optic nerve head-retinal nerve fiber layer analysis with spectral-domain optical coherence tomography of ethambutol-induced ocular toxicity in patients on a daily regime of anti-tubercular therapy

ABSTRACT

Purpose: This study aims to analyze the clinical profile of patients who presented with visual symptoms after the onset of anti-tubercular therapy (ATT) on daily fixed drug combination and to quantify optic nerve damage in these patients using optical coherence tomography as an objective tool. **Study Design and Methodology:** This was a cross-sectional observational study of 20 patients who presented with visual symptoms following treatment with daily regime ATT. History was recorded, and detailed ophthalmological evaluation was done, including optic nerve head-retinal nerve fiber layer (ONH-RNFL) analysis using spectral-domain optical coherence tomography (SD-OCT). Data were analyzed with PSPP software. **Results:** Patients received ethambutol (EMB) at a mean daily dose of 17.61 ± 1.73 mg/kg/day. Of the 40 eyes analyzed, color vision was defective in 35 eyes and contrast sensitivity was reduced in 27 eyes. Mean ONH-RNFL thickness values were 110.8 ± 26.5 μm; 103.7 ± 24.4 μm; 72.6 ± 18 μm; 63.9 ± 13.2 μm; in the inferior, superior, nasal, and temporal quadrants, respectively. Females had more RNFL loss than males. Age, weight, and contrast sensitivity had a positive correlation and log mar vision had a negative correlation with RNFL thickness. Duration of EMB therapy, cumulative dose, and indication for ATT influenced ONH-RNFL thickness. History of renal disease, alcoholism, and smoking were risk factors for RNFL loss. There was a median delay of 21 days in reporting after the development of visual symptoms. **Conclusions:** Our study population received EMB at a daily dose of >15 mg/kg/day. ONH-RNFL thickness was reduced on SD-OCT. RNFL thickness helps to quantify the role of various risk factors in EMB toxicity, making it a useful tool for objective assessment. Patient education and active screening for the detection of early toxicity are needed to reduce visual impairment and blindness.

Keywords: Daily regime anti-tubercular therapy, ethambutol toxicity, optic nerve head-retinal nerve fiber layer, spectral-domain optical coherence tomography

INTRODUCTION

As per global tuberculosis (TB) report 2019, the estimated incidence of TB in India was approximately 2,690,000 with 130,000 cases of multidrug-resistant tuberculosis.[1] The Standards for TB Care in India 2014 based on available evidence and Treatment of TB Guidelines by the WHO (2010), state that all TB patients be given a daily regimen of anti-tubercular therapy (ATT) which requires the patient to be on ethambutol (EMB) for 6 months or more as opposed to the previous regime where EMB was not a part of the continuous phase in all patients and EMB was administered at a dose of 15 mg/kg/day. In the new regime of ATT, patients

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are divided into four weight bands of 25–39 kg; 40–54 kg; 55–69 kg and ≥70 kg receiving 550 mg; 825 mg; 1100 mg and 1375 mg of EMB daily, respectively.[2] This modification to counteract drug resistance has resulted in an increase in the number of patients on ATT presenting with features of ATT-induced toxic optic neuropathy. This study aims to analyze the clinical profile of these patients and to quantify optic nerve damage in these patients using optical coherence tomography as an objective tool.

Aims and objectives

Our study aims to analyze the clinical profile of patients who presented with visual symptoms after the onset of ATT, to assess optic nerve head retinal nerve fiber layer (ONH-RNFL) thickness in patients who were on EMB as part of the revised daily regime of anti-tubercular therapy (RNTCP) and the effect of various risk factors on RNFL thickness.

MATERIALS AND METHODOLOGY

This is a descriptive cross-sectional study of patients who were referred to the ophthalmology outpatient department of a tertiary health care center in North Kerala with decreased visual functions following treatment with ATT on daily regime. Patients with pulmonary and extrapulmonary tuberculosis on daily regime ATT who presented with complaints of defective vision following treatment with daily regime ATT were included in this study. Patients with TB meningitis, suspected ocular tuberculosis, those with defective visual acuity and color vision prior to initiation of ATT and patients with co-existent ocular pathology which could independently affect visual function were excluded from this study. The study period was 1 year.

After approval from the institutional ethics and research committee and after obtaining informed consent, patients who presented with complaints of defective vision following treatment with daily regime ATT were examined in detail. History of symptoms, comorbid conditions and drug history were recorded. Detailed ophthalmological examination was carried out, including best-corrected visual acuity (BCVA) with Snellen chart, which was recorded in logmar values. Based on the BCVA, patients were divided into groups based on the International Classification of Diseases for visual impairment. Pupillary reactions were recorded as brisk or sluggish reaction to light. Color vision was tested with Ishihara color plates at a distance of 75 cm. Out of 21 plates, if the patients reads ≥17 plates correctly, color vision was recorded as normal. Contrast sensitivity was measured with the Pelli-Robson chart at 1 m distance. A value of ≥1.5 was considered as normal and <1.5 was taken as reduced contrast sensitivity. The dilated retinal evaluation was done with 90 D slit-lamp biomicroscopy and direct ophthalmoscopy. Optic disc findings were recorded as pink or pale neuroretinal rim (NRR).

ONH-RNFL thickness assessment was done with OPKO-OTI spectral-domain optical coherence tomography (SD-OCT) machine. The RNFL thicknesses in the normal range are represented by green backgrounds, those that are abnormal at the 5% level are represented by yellow backgrounds, and those that are abnormal at the 1% level are represented by red backgrounds. White color code refers to values above normal. Values in yellow and red background represented RNFL thinning. Data were analyzed using PSPP software (Free Software Foundation (2015). GNU PSPP (Version 0.8.5) [Computer > Software]. Boston, MA). Statistical analysis performed included independent sample *t*-test, one-way analysis of variance (ANOVA) and tests for bivariate correlation. $P < 0.05$ was considered as statistically significant, and $P > 0.05$ was taken as not statistically significant.

RESULTS

Twenty-one patients satisfied the inclusion criteria. Of this, one patient was excluded from the study as she was not on fixed drug combination. OCT recording could not be done in one eye due to the inability of the patient to fix. Hence, 39 eyes of 20 patients were analyzed. Mean age of the study population was 52.1 ± 15.2 years with a range from 15 to 75 years. Male-female ratio was 1:1. Patients received EMB for median duration of 180 days (87–357). Visual symptoms started after a median delay of 151 days (37–251) of therapy with EMB. The median delay from the onset of visual symptoms to seeking medical attention was 21 days (3–120 days). Of the 20 patients, only 5 patients reported within 1 week of onset of visual symptoms.

The dosage of EMB was calculated based on the weight band of the patient. This distribution is given in Table 1. The mean weight of the study group was 58.8 ± 14.8 kg with a range from 35 to 90 kg.

The indications for starting ATT were pulmonary TB in 8 patients and extra pulmonary in 12 patients. The extrapulmonary indications were TB spine ($n = 5$), TB pleural effusion ($n = 3$), epidural abscess ($n = 1$), lupus vulgaris ($n = 1$), ileocecal TB ($n = 1$), genitourinary TB ($n = 1$), and TB lymphadenitis ($n = 1$). Patients with pulmonary TB received EMB for a mean duration of 166.3 ± 64.8 days as compared to 187.8 ± 76.6 days in those with extra pulmonary TB (P 0.589).

On testing for visual acuity, 13 eyes had vision accounting to visual impairment (20/70–20/400) and 19 eyes had vision

accounting to blindness (<20/400). Eight eyes had normal visual acuity (20/20–20/60). Of the 40 eyes analyzed, color vision checked with Ishihara's chart was defective in 35 eyes. Contrast sensitivity assessed with Pelli-Robson chart was reduced in 27 eyes. Mean contrast sensitivity in the study population was 0.94 ± 0.6 (0–1.8).

On examination for pupillary reaction to light, 33 eyes had sluggish reaction to light and 6 eyes had brisk reactions. On analysis of optic disc, 26 eyes had pallor of NRR and 13 eyes had pink NRR.

Mean ONH-RNFL thickness values were 110.8 ± 26.5 μm; 103.7 ± 24.4 μm; 72.6 ± 18 μm; 63.9 ± 13.2 μm; in the inferior, superior, nasal, and temporal quadrants, respectively. Valuesseen in <5% of the normal population was taken as thinning (yellow and red color background on OCT). Of the 40 eyes analyzed 28 eyes showed ONH-RNFL thinning on OCT depicted in the yellow and red background [Figure 1] and 4 showed thickening of RNFL depicted in white background [Figure 2]. ONH-RNFL was normal in 7 eyes [Figure 3]. Of the 40 eyes, analyzed 17 eyes had RNFL thinning in superior quadrant, 14 in inferior, 12 in temporal quadrant and 10 in nasal quadrant.

Correlation of ONH-RNFL thickness with age and weight is depicted in Table 2. Mean ONH-RNFL values are given in Table 3. Younger patients had lower RNFL values. Patients who weighed less had more ONH-RNFL loss, which was statistically significant in 2 quadrants. The ONH-RNFL thickness was less in females as compared to males in all 4 quadrants. The distribution of patients across the 4 weight bands is depicted in Table 1. On doing an ANOVA one-way test to analyze ONH-RNFL thickness across patients of different weight bands, there was a progressive reduction of RNFL thickness in the lower weight bands. The values were statistically significant in superior (*P* value < 0.001) inferior (*P* 0.048) and temporal quadrants (*P* 0.008) [Table 4]. Patients at the lower end of the weight spectrum had more thinning of ONH-RNFL.

Patients received EMB at a mean daily dose of 17.61 ± 1.73 mg/kg/day. Patients belonging to all four weight categories had received EMB at a daily dose >15 mg/kg/day. The difference in EMB/kg body weight across the 4 weight bands was statistically significant on doing a one-way ANOVA test (*P* 0.007).

As shown in Table 3, mean ONH-RNFL thickness was less in superior (*P* 0.095) and inferior quadrants (*P* 0.230) of those with extra-pulmonary TB as compared to those with pulmonary TB.

The patients with normal findings on OCT (*n* = 7) had received EMB for a shorter duration (152.1 ± 55.7 days) as compared to those with abnormality on OCT (185.8 ± 75.5 days). They had received a lower cumulative dose of EMB (152.4 ± 64.8 g) than those with abnormal OCT (191.2 ± 84.2 g). These

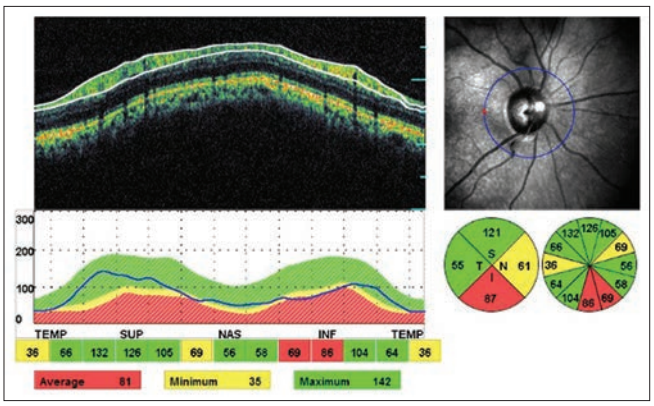


Figure 1: Spectral domain optical coherence tomography image of patient showing retinal nerve fibre layer thinning on optic nerve head-retinal nerve fibre layer scan

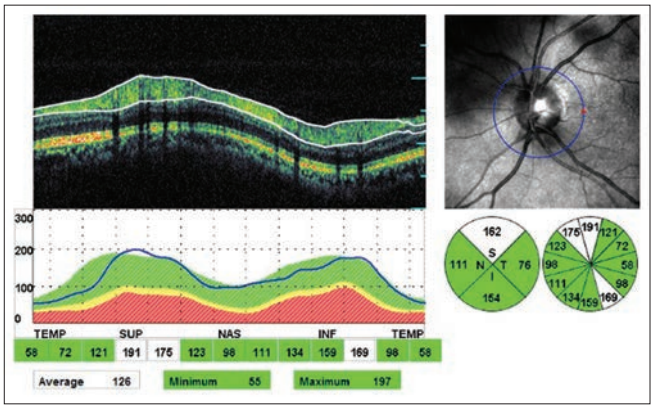


Figure 2: Spectral domain optical coherence tomography image of patient showing retinal nerve fibre layer thickening on optic nerve head-retinal nerve fibre layer scan

Table 1: Mean values of ethambutol dose across different weight bands

Weight band (kg)	*n* (%)*	Daily dose of ethambutol (mg)	Average weight (kg)	Average dose per kg body weight per day (mg/kg/day)
25-39	2 (10)	550	36.5±2.1	15.09±0.88
40-54	5 (25)	825	46.6±4.2	17.82±1.58
55-69	9 (45)	1100	60.7±4.2	18.21±1.25
70+	4 (20)	1375	80.8±11.2	17.28±2.36

*Number of eyes

findings were not statistically significant. The mean delay in recording OCT was 57 ± 24.3 days in those with abnormal thickening of RNFL as compared to 152.5 ± 132.6 days in those with RNFL loss (*P* 0.003). RNFL thickening was seen in patients who presented early.

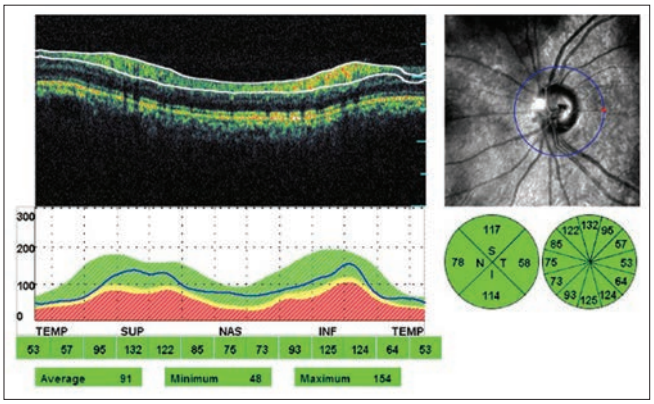


Figure 3: Spectral domain optical coherence tomography image of patient showing retinal nerve fibre layer of normal thickness on optic nerve head-retinal nerve fibre layer scan

The correlation of ONH-RNFL thickness with logmar vision and contrast sensitivity is depicted in Table 2. Mean ONH-RNFL values are depicted in Table 3. The ONH-RNFL loss was more in patients with impaired vision or blindness as compared to those with normal vision (*P* >0.05). Scatterplot chart of ONH-RNFL thickness versus logmar vision showed negative trendline in superior, inferior, and nasal quadrants [Graph 1]. With the worsening of vision, there was the reduction of ONH-RNFL thickness. As shown in Table 2 there was the reduction of ONH-RNFL thickness with reduction of contrast sensitivity which was statistically significant in superior (*P* 0.007) and inferior quadrant (*P* 0.047). Positive trendline was seen on scatterplot in the superior, inferior, and nasal quadrant [Graph 2].Contrast sensitivity was 1.26 ± 0.36 in those with normal OCT ($n = 7$) and 0.9 ± 0.61 in those with abnormal OCT ($n = 32$). Contrast sensitivity was 1.31 ± 0.31 in patients with thickening of ONH-RNFL ($n = 4$) and 0.84 ± 0.62 in patients with thinning of ONH-RNFL ($n = 28$). Mean ONH-RNFL thickness was more in patients with normal contrast sensitivity as compared to

Table 2: Bivariate correlation of optic nerve head-retinal nerve fiber layer thickness in 4 quadrants with quantitative variables

Variable	Superior quadrant†	*P*	Inferior quadrant†	*P*	Nasal quadrant†	*P*	Temporal quadrant†	*P*
Age	−0.5	0.761	0.21	0.202	0.27	0.099	0.09	0.581
Weight	0.53	0.001	0.31	0.057	0.28	0.085	0.43	0.007
Contrast sensitivity	0.43	0.007	0.32	0.047	0.26	0.114	−0.04	0.809
Logmar vision	−0.36	0.024	−0.11	0.518	−0.19	0.255	−0.11	0.499

†Pearson correlation

Table 3: Independent sample *t*-test to compare mean optic nerve head-retinal nerve fiber layer thickness in 4 quadrants classified on the basis of qualitative variables

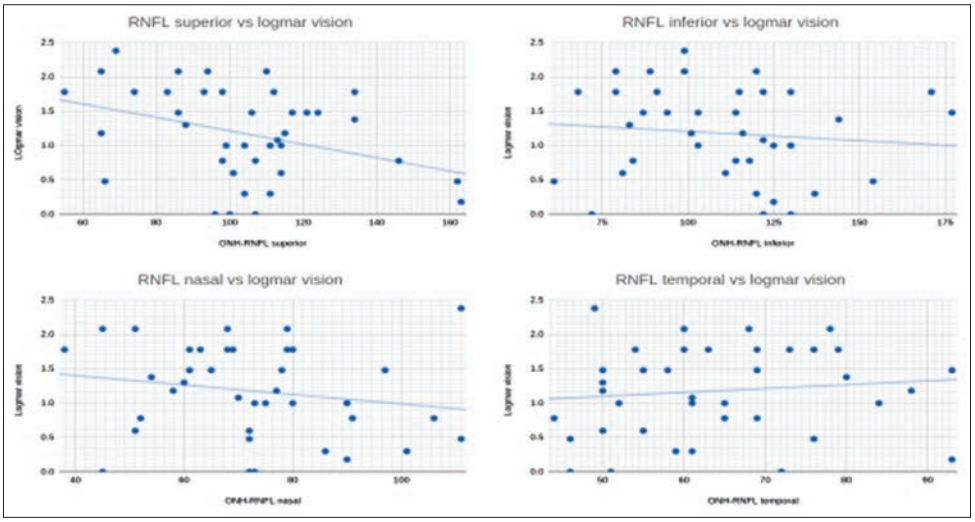
Variable	Value	*n**	Superior quadrant‡ (μm)	Inferior quadrant‡ (μm)	Nasal quadrant‡ (μm)	Temporal quadrant‡ (μm)
Gender	Male	10	111.2±28.7	118.4±30.4	75.9±20.3	64.6±15.3
	Female	10	96.6±17.4	103.6±20.4	69.6±15.3	63.2±11.2
	P		0.061	0.080	0.160	0.068
Indication	Pulmonary	16	107.5±18.3	111.4±21.3	71.6±17.8	61.2±13.8
	Extra-pulmonary	23	101.1±28	110.4±30	73.4±18.4	65.8±12.7
	P		0.095	0.230	0.990	0.640
Vision	≤20/60	8	113.6±33.1	115.1±32	81.3±20.5	63±16.4
	>20/60	31	101.2±21.6	109.7±25.4	70.4±16.9	64.1±12.6
	P		0.208	0.474	0.528	0.349
Contrast sensitivity	Normal	13	116±26.9	110.9±27.3	77.6±17.3	62.5±14.8
	Reduced	26	97.6±21	110.7±26.6	70.2±18.1	64.6±12.6
	P		0.024	0.980	0.980	0.656
Pupil	Brisk	6	113±17	119±19.3	83.2±12.5	65±12.3
	Sluggish	33	102±25.4	109.3±27.6	70.7±18.3	63.7±13.5
	P		0.258	0.296	0.489	0.783
Colour vision	Normal	5	121.8±30.6	104.6±24.7	77±19.3	64±18.5
	Defective	34	101.1±22.7	111.7±26.9	72±17.9	63.9±12.6
	P		0.076	0.584	0.608	0.608
Disc	Pink NRR	13	123.7±22.4	129.7±28	81.2±15.6	72.1±13.9
	Pale NRR	26	93.7±18.8	101.3±20.2	68.4±17.8	59.8±10.9
	P		0.000	0.001	0.033	0.005

*Number of eyes, ‡Mean ONH-RNFL thickness. NRR - Neuro retinal rim, ONH-RNFL - Optic nerve head-retinal nerve fiber layer

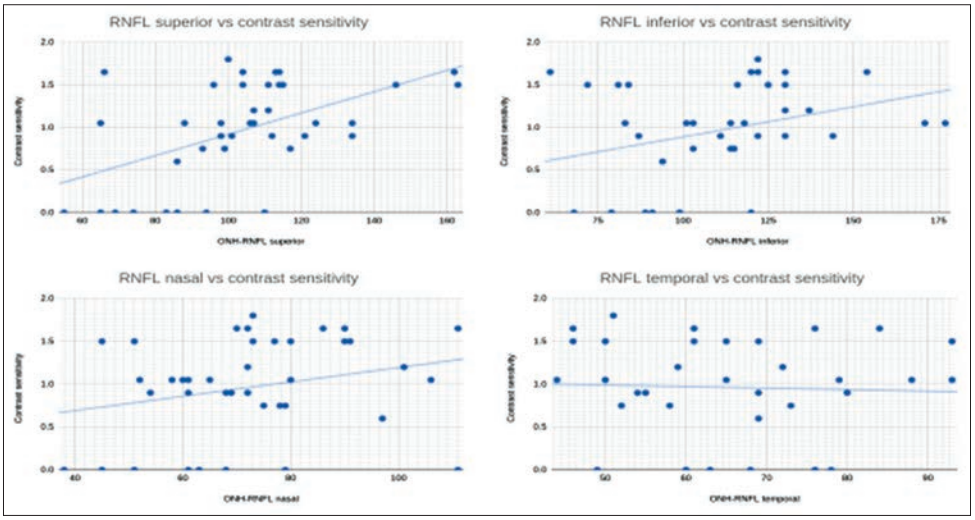
Table 4: One-way ANOVA test to compare mean optic nerve head-retinal nerve fiber layer thickness in 4 quadrants across different weight bands

Weight band (kg)	n*	Superior quadrant (μm)‡	Inferior quadrant (μm)‡	Nasal quadrant (μm)‡	Temporal quadrant (μm)‡
25-39	4	106.00±16.51	90.50±9.29	58.50±5.00	53.75±4.79
40-54	10	87.80±21.89	104.30±26.44	71.30±18.66	64.60±9.96
55-69	17	98.29±14.70	109.88±18.65	73.65±18.72	60.06±12.47
70+	8	134.00±22.90	130.88±36.27	79.25±17.92	76.25±13.58
Total	39	103.72±24.41	110.77±36.27	72.64±17.95	63.90±13.21
P		0.000	0.048	0.307	0.008

*Number of eyes, ‡Mean ONH-RNFL thickness. ONH-RNFL - Optic nerve head-retinal nerve fibre layer



Graph 1: Scatterplot chart of optic nerve head-retinal nerve fibre layer thickness versus Logmar vision. x axis- optic nerve head – retinal nerve fibre layer thickness in µm. y axis - logmar vision



Graph 2: Scatterplot chart of optic nerve head-retinal nerve fiber layer thickness versus contrast sensitivity. x axis- optic nerve head – retinal nerve fibre layer thickness in µm. y axis - contrast sensitivity value

patients with reduced contrast sensitivity. This finding was statistically significant in the superior quadrant (*P* 0.024).

Mean ONH-RNFL values as obtained in each quadrant when analyzed in relation to color vision, pupillary reaction, and color of the neuroretinal rim are depicted in Table 3.

Mean ONH-RNFL was reduced in those with defective color vision as compared to those with normal color

vision ($P > 0.05$). ONH-RNFL loss was more in eyes with sluggish pupillary reactions as compared to those with brisk reactions ($P > 0.05$). Patients with pale NRR had more RNFL loss in all quadrants as compared to those with pink NRR ($P < 0.05$).

On analyzing role of co-morbidities and addictions, the following observations were made. Values are given in Table 5. Mean ONH-RNFL thickness was more in diabetics and hypertensives. This finding was statistically significant in the temporal quadrant (P 0.032) in hypertensives. The mean ONH-RNFL value was less in patients with renal disease when compared to those without renal disease ($P > 0.05$) ONH-RNFL was reduced in smokers as compared to nonsmokers. Finding in the nasal quadrant was statistically significant (P 0.018). The mean ONH-RNFL thickness was reduced in alcoholics in all four quadrants as compared to nonalcoholics ($P > 0.05$).

DISCUSSION

EMB hydrochloride was introduced as a chemotherapeutic agent in tuberculosis in 1961. The mechanism of action of EMB is believed to be an alteration of the mycobacterial cell wall structure.[3,4] EMB has an established place as a first-line antituberculosis agent, valued for the protection that it offers companion drugs against the development and consequences of drug resistance. The ocular side effects of EMB include optic neuritis,[5] Red-green color blindness[6] and vertical nystagmus. Retrobulbar neuritis is the most common type of optic neuritis seen. Clinically, EMB-induced optic neuropathy presents with simultaneous bilateral involvement. However, the onset may be unilateral, but eventually, both eyes are involved. The gradual onset and slow progression of the symptoms may delay detection with a consequent delay in management.

The incidence of EMB induced optic neuropathy has been studied extensively. In a study by Tiwari and Mishra 269 smear-positive pulmonary tuberculosis patients receiving 20 mg/kg body weight of EMB were analyzed and they found optic nerve involvement in 2.2% of the patients.[7] Whereas in a study by Narang and Varma retrobulbar neuritis was found in four of the 640 cases (0.62%) studied.[8] In a study by Griffith D E eight of 139 patients (6%) on daily therapy were diagnosed with EMB ocular toxicity, whereas none of the 90 patients on intermittent therapy had EMB ocular toxicity ($P = 0.05$).[9] EMB ocular toxicity was more common when the patient was on daily therapy as compared to intermittent therapy.

Optical coherence tomography (OCT) is a noninvasive imaging technology used to obtain high-resolution cross-sectional images of the retina. Retinal thickness can be measured to aid in the early detection and diagnosis of retinal diseases and conditions. OCT has been extensively used to quantify RNFL defects in patients with EMB toxicity. The peripapillary RNFL thickness was determined by SD-OCT in a study by Alasil *et al*. in 200 healthy patients and mean RNFL thickness values were 120 ± 20.5, 112 ± 18.5, 72.5 ± 16, and 71 ± 14 μ for the

Table 5: Independent sample *t*-test to compare mean optic nerve head-retinal nerve fiber layer thickness in 4 quadrants classified on basis of comorbidities and addictions

Factor	*n**	Superiorquadrant (μm)‡	Inferior quadrant (μm)‡	Nasal quadrant (μm)‡	Temporal quadrant (μm)‡
DM					
Yes	21	103.5±24	114.2±27.7	72.6±15.6	66.1±13.3
No	18	104±25.6	106.7±25.1	72.7±20.8	61.3±13.0
P		0.774	0.852	0.26	0.711
HTN					
Yes	9	113.4±34.2	114.8±20.2	82.9±20.3	68.2±17.1
No	30	100.8±20.5	109.6±28.3	69.6±16.3	62.6±11.8
P		0.139	0.224	0.314	0.032
Renal disease					
Yes	5	93±16.6	103.8±19.5	81.6±23.5	62.4±8.4
No	34	105.3±25.2	111.8±27.4	71.3±17.1	64.1±13.9
P		0.439	0.461	0.355	0.134
Smoking					
Yes	11	104.2±34.1	104.9±24.3	71.1±15.2	60.1±15.9
No	28	103.5±20.2	113.1±27.4	76.5±24.1	65.4±12
P		0.087	0.499	0.018	0.199
Alcoholism					
Yes	4	89.5±28.4	87.5±18.9	59.8±11.1	57.3±14.3
No	35	105.3±23.9	113.4±26.1	74.1±18.1	64.7±13.1
P		0.223	0.062	0.072	0.294

*Number of eyes, ‡Mean ONH-RNFL thickness. ONH-RNFL - Optic nerve head-retinal nerve fiber layer, HTN - Hypertension

inferior, superior, nasal, and temporal quadrants, respectively.[10] ONH RNFL thickness was significantly reduced among our study subjects who developed defective vision while on ATT.72% of the cases ($n = 28$) showed thinning of ONH-RNFL on SD-OCT. Similarly, there was a significant reduction in the thickness of the nerve fiber layer by OCT in the study by Pavan Taffner *et al*., which was more pronounced in those on the extended treatment regimen.[11] There was considerable NFL loss, especially of the temporal fibers in 3 patients with EMB-induced optic neuropathy studied by Zoumalan *et al*.[12] They concluded that OCT can be a valuable tool in the quantitative analysis of optic neuropathies. Kim and Ahn studied seven patients (14 eyes) with a history of EMB-induced optic neuropathy and detected a decrease in RNFL thickness in all eyes with the greatest decrease in the temporal quadrant.[13]

10.3% of our cases ($n = 4$) showed an abnormal increase in the thickness of RNFL. Similar findings were obtained by Kim and Hwang[14] who found a relative thickening of temporal RNFL that might be accounted a mild swelling of the papillomacular bundle. The patients in whom RNFL thickening was detected had presented earlier than those with RNFL loss .RNFL thickening could be a sign seen in the early stages of EMB toxicity due to edema of nerve fiber layer while gradually leads to loss of retinal nerve fiber layer and hence thinning on OCT.

The effect of various risk factors on ATT-induced ocular toxicity was analyzed by quantifying the ONH-RNFL loss in each group. Age and weight had a positive correlation with ONH-RNFL. Younger age and lower weight were associated with more RNFL loss. Patients at the lower end of the weight spectrum had more thinning of ONH-RNFL. This could be because in the current dosage regimen, a patient weighing 25 kg receives 550 mg of EMB/day, which comes up to 22 mg/kg/day, while a patient weighing 39 kg receives the same 550 mg accounting for 14.10 mg/kg/day. Hence, patients at the lower end of weight band receive a higher dose of EMB. This coupled with the more prolonged duration of treatment with EMB produces a higher cumulative dose in these patients. On analyzing the daily dose per kg body weight in our study, it was found to be >15 mg/kg body weight in patients belonging to all weight bands. The patients with an abnormality on OCT had received EMB for a longer duration and received a higher cumulative dose of EMB. Patients with extra-pulmonary TB received EMB for a longer duration and had more RNFL loss as compared to those with pulmonary TB. Age, duration of EMB, and dose of EMB were positively correlated with the risk of toxicity in a study conducted by Talbert Estlin and Sadun[15] Medication duration was shown to be a strong risk factor for the occurrence of subclinical toxicity in a study by Jin *et al*.[16] Mean RNFL loss was less in diabetics and hypertensives and more in patients with renal disease, history of smoking and alcoholism. Age, hypertension and renal diseases were risk factors for optic neuropathy in the Taiwanese population in a study by Chen *et al*.[17] A low dose and prompt discontinuation of the drug was recommended, particularly in individuals with diabetes mellitus, glaucoma or who are heavy smokers.[18] Study by Kanaujia *et al*. concluded that EMB should be avoided in renal disorder patients in view of the high incidence of toxic optic neuropathy.[19] Renal failure prolongs the elimination half-life of EMB and increases the risk of EMB-induced optic neuritis. EMB toxicity has been identified as being dose-related, with a reported incidence of 18% in patients receiving >35 mg/kg/day, 5%–6% with 25 mg/kg/day, and <1% with 15 mg/kg/day of EMB, for more than 2 months.[20]

The relation of visual functions to ONH-RNFL thickness revealed the burden of visual disability in the patients affected with EMB toxicity. As expected RNFL loss was more in eyes with impaired vision, defective color vision, reduced contrast sensitivity, and sluggish pupillary reactions to light.

Previous studies show that ONH-RNFL loss was more significant in the cases that presented changes in the Ishihara test.[11] In patients treated with EMB, disturbances in color vision may be the first and only symptoms of the onset of toxic damage to the optic nerves.[21] In the study by Tiwari and Mishra color blindness was not a prominent feature.[7]

In our study, we found a median delay of 21 days in seeking medical attention after onset of visual symptoms. This stresses the need for proper patient education regarding the potential side effects of ATT and the need to seek immediate medical help when faced with visual symptoms. Sivakumaran *et al*. have said that impaired communication was potentially very important in cases of EMB toxicity, and special care was needed in educating patients about EMB.[22] This points to the need for proper awareness among physicians to teach patients started on ATT about the possible ocular complications and to ask them about any visual complaints at each visit. Having an Ishihara chart at each drug distribution center and screening at each visit would be a cost-effective method to detect ocular toxicity early and to provide a better visual outcome for these patients.

CONCLUSIONS

Our study population received EMB at a daily dose of >15 mg/kg/day. ONH-RNFL thickness was reduced on SD-OCT. Females had more RNFL loss than males. Age, weight, and contrast sensitivity had positive correlation, and

logmar vision had a negative correlation with RNFL thickness. Duration of EMB therapy, cumulative dose, and indication for ATT influenced the presence of RNFL thinning. Patients with a history of renal disease, alcoholism and smoking had more RNFL loss. Patients with pale NRR and defective color vision had more RNFL loss. Patients showed delay in reporting after the development of visual symptoms. Patient education and active screening for the detection of early toxicity are needed to reduce visual impairment and blindness.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Analysis of foveal microvascular abnormalities in various stages of diabetic retinopathy using optical coherence tomography angiography

ABSTRACT

Purpose: Diabetic retinopathy (DR) remains a leading cause of vision loss in the adult population. The purpose of our study was to analyze and co-relate diabetic retinopathy-related micro-vascular changes using Optical Coherence Tomography Angiography (OCTA) in various stages of diabetic retinopathy. **Methods:** One hundred and twenty eyes of diabetic patients were categorized into three groups of forty each. Group-A included eyes without retinopathy, Group-B included eyes with Non-Proliferative Diabetic Retinopathy and Group-C included eyes with proliferative DR. Apart from complete ocular examination, foveal avascular zone parameters were analyzed using OCTA. **Results:** Statistically significant differences were found concerning vascular density and perfusion density between eyes with DR when compared to eyes without DR (P>0.001). 9 Vascular density (VD) significantly decreases in eyes with the progressive stage of DR. Foveal avascular zone showed a significant increase in area, perimeter, and circularity in the eyes with PDR compared to other groups. **Conclusion:** FAZ metrics showed significant changes proportional to diabetic retinopathy stages. Vascular density and perfusion density parameter analysis by OCTA could be used as early biomarkers in predicting the risk of diabetic retinopathy progression.

Keywords: Diabetic macular edema, diabetic retinopathy, foveal avascular zone, optical coherence tomography angiography, superficial capillary plexus, vessel density

INTRODUCTION

Diabetic retinopathy is the leading cause of blindness worldwide owing to its microvascular complications. The predicted worldwide prevalence of diabetes in the recent scenario may reach 430 million by 2030.[1] The long duration of diabetes and poor glycemic control are the major risk factors for retinopathy. Early diagnosis is imperative in preventing the sight-threatening complications. Sight-threatening complications occur as a result of macular involvement, such as in diabetic macular edema (DME) or diabetic macular ischemia (DMI) and due to the development of the proliferative disease. Mere slit lamp bio-microscopy screening may miss retinopathy changes in diabetic patients. Although fluorescein angiography provides functional information regarding the leakage of dye to provide information on the permeability of vessels, it is an invasive procedure with the added risk of the procedure and dye-related events. Repeating the invasive above procedure among renal and cardiac patients is also an additional risk.

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Optical coherence tomography angiography (OCTA) is a promising new noninvasive imaging technique that employs motion contrast imaging to high-resolution volumetric blood flow information generating angiographic images. It compares the differences in backscattered OCT signals between sequential scans. Erythrocyte movement in sequences of B-scans is utilized to map retinal vessels. Also, OCTA is a noninvasive technique that acquires volumetric angiographic information without the usage of dye. The en-face images (OCT angiograms) can then be scrolled outward from the internal limiting membrane to the choroid to visualize the individual vascular plexus and segment the inner retina, outer retina, choriocapillaris, or other areas of interest.[2]

In diabetic retinopathy, OCTA can detect microaneurysms, intraretinal microvascular abnormalities, nonperfusion areas, and neovascularization, and it is able to offer additional information with respect to the localization of these changes. Thus OCTA offers added advantage in detecting microvascular changes even before changes are apparent in the fundoscopic examination.

OCTA has previously been used to describe retinal microvascular lesions in diabetic patients and helps to diagnose macular ischemia.[3] In diabetic patients, macular microvascular changes like asymmetry and enlargement in the foveal avascular zone (FAZ) area, are reported in the literature, in the absence of diabetic retinopathy changes clinically.[4,5] Quantitative assessments that can be measured in OCTA are, vessel density and perfusion density, which help in better understanding of the pathophysiology, disease activity and help deciding appropriate treatment and follow-up of DR patients.[6]

The aim of this study is to assess the characteristics of foveal microvascular abnormalities in different stages of Diabetic retinopathy. In this study, several OCTA-based macular vascular parameters were analyzed and the results were compared between the eyes without Diabetic Retinopathy, eyes with different stages of diabetic retinopathy i.e., nonproliferative diabetic retinopathy (NPDR), and PDR.

MATERIALS AND METHODS

An observational cross-sectional study was done to evaluate microvascular changes in diabetic patients attending the retina department of our tertiary care center. The study period was from January 2019 to 2020. The study population included 120 eyes among 72 patients. Majority of study patients were type 2 diabetics. The patients underwent comprehensive ocular examination, including visual acuity, slit-lamp biomicroscopy, fundoscopy, OCT, and OCTA. Diabetic retinopathy grades were based on the Early Treatment Diabetic Retinopathy Study classification.[7] Study eyes were accordingly divided into 3 groups - Group A, B, and C. Each group had forty eyes. Eyes with no frank manifestations of the diabetic retinopathy, neither on clinical examination nor on the common diagnostic tools were included in Group A. While eyes with NPDR changes were included in Group B. And Group C included eyes with PDR.

Inclusion criteria were patients with diabetes mellitus (both type 1 and type 2) with and without diabetic retinopathy. The eyes with diabetic macular edema at any stage of DR and phakic eyes with early cataract changes i.e., grading between NSI to NSII, with media clarity sufficient for good quality OCT/OCTA were included.

Exclusion criteria were eyes with the presence of dense media opacity due to cataract, vitreous hemorrhage, Pseudophakia with dense posterior capsular opacification, macula changes associated with vitreomacular traction, and macular tractional retinal detachment. Eyes that had received previous laser photocoagulation, intravitreal anti-VEGF/triamcinolone injections, and eyes with the history of vitreoretinal surgery in the past were also excluded.

OCT and OCTA were performed to assess the state of patients' neurosensory retina and retinal vasculature. Optical coherence tomographic angiography was performed with a Zeiss CIRRUS™ HD-OCT Model 5000, imaging instrument using the optical microangiography algorithm (Carl Zeiss Meditech). The standard scanning patterns that are available while using ZEISS Angioplex™ OCT angiography include cube scans of 3 mm × 3 mm and 6 mm × 6 mm, along with an increased scan rate of 68,000 A-scans per second and FastTrac™ retinal-tracking technology, for motion correction and reproducible follow-up positioning of scans. The eyes of each participant were scanned with B-scans composed of 1000 A-scans (for Macular Cube 200 × 200) or 1024 A-scans (for Macular Cube 512 × 128). The inner retina was estimated as being the tissue between the inner limiting membrane and an offset from the retinal pigment epithelium of 110 μm. The superficial retinal layer (SRL) was defined as the inner 70% of the inner retina, and the deep retinal layer was the remaining 30% of the inner retina. Scanning results in either a 6 mm × 6 mm/3 mm × 3 mm square cube, similar to the macular 512 × 128/200 × 200 cubes but uses an intensity-based frequency filtering technique to generate images with detailed vasculature.

The FAZ measurements were based on the SRL. The area and perimeter of this zone were calculated, and the circularity

index was calculated as $4\pi A/P$, where A is the area and P is the perimeter. The area contained within the boundary of the FAZ mm^2. FAZ perimeter the length of the boundary of the FAZ mm. FAZ Circularity How similar the boundary of the FAZ is to a circle. Values range from 0 to 1. A value of 1 means the FAZ forms a perfect circle while a value near zero means that the boundary of FAZ is very different from a circle. All these calculations are performed with the inbuilt software commercially available on the Cirrus high-definition–OCT with AngioPlex [Figure 1a].

Vascular density was measured using binary reconstruction of images and was defined as the percentage of the sample area occupied by vessel lumens. The percentage of vessels was further measured in each sector (superior, temporal, inferior, and nasal) based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart with the foveal center being automatically determined from the relevant OCT data. The inner and outer rings with a diameter of 1 and 2.5 mm centered on the fovea were respectively considered for evaluation representing the central 10 degree of the visual field. Density and perfusion values were assessed using in-built OCTA software and ETDRS chart overlay was used to calculate perfusion density (PD in percentage) and vessel density (VD mm/mm^2) in all quadrants around the fovea [Figure 1b].

Statistical analysis

Statistical analysis was done using SPSS version 21.0. All the data were analyzed by descriptive statistics, such as mean and standard deviation. Independent *t*-test and Chi-square test were used to compare data between the groups. Multivariate analysis was performed to investigate the correlation of FAZ parameters in various stages of diabetic retinopathy. $P < 0.05$ was considered statistically significant.

RESULTS

Our study consisted of 8 (12%) patients with type 1 diabetes and 64 (88%) patients with type 2 diabetes [Table 1]. The study included 40 eyes in each group, the male and female sex ratio was comparable in all three groups. The duration of diabetes varied in each group, in groups with no DR 80% were <5 years, group with NPDR 50% between 5 and 10 years, and group with PDR 45% of patients had diabetes greater then15 years. The mean duration of diabetes in the NPDR group was 9.80 ± 6.48 years compared to the PDR group 12.12 ± 6.48 years. The difference in the

Table 1: Description of demographic and clinical parameters (mean±standard deviation)

Parameters	Group B (NPDR), *n* (%)	Group C (PDR), *n* (%)	*P*
Age (years)	54.90±9.17	58.98±9.64	0.056
Sex (male/female)	12/12	14/12	
Duration of DM (years)	9.80±6.48	12.12±4.81	0.048
HT (patients)	10 (41.6)	14 (53.8)	
DME (number of eyes)	20 (50)	18 (45)	
CMT (microns)	360.63±160.65	333.38±105.23	0.372
SMD (number of eyes)	8 (20)	7 (17.5)	

P<0.05 is statistically significant. NPDR – Nonproliferative diabetic retinopathy, PDR – Proliferative diabetic retinopathy, DM – Diabetes mellitus, DME – Diabetic macular edema, SMD – Serous macular detachment, CMT – Central macular thickness, HT – Hypertensive patients in each group

Table 2: (a) Comparison of vision groups for nonproliferative diabetic retinopathy (b) comparison of vision groups for proliferative diabetic retinopathy

	Vision (logmar), mean±SD	*P*
(a) NPDR group, number of eyes		
DME (*n*=20)	0.32±0.21	0.480
No DME (*n*=20)	0.20±0.17	
(b) PDR group, number of eyes		
DME (*n*=18)	0.37±0.24	0.401
No DME (*n*=22)	0.44±0.25	

In comparison, *P*-value being >0.05, suggesting vision wise there was no difference between the groups. SD – Standard deviation, NPDR – Nonproliferative diabetic retinopathy, DME – Diabetic macular edema, PDR – Proliferative diabetic retinopathy, Logmar – Logarithm of the minimum angle of resolution

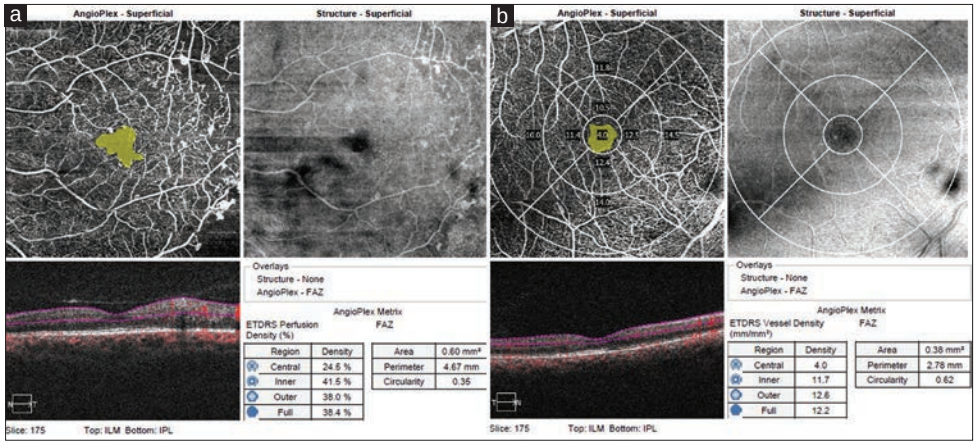


Figure 1: (a) Nonproliferative diabetic retinopathy eye with altered foveal avascular zone parameters and vessel density, (b) proliferative diabetic retinopathy eye with altered foveal avascular zone parameters and perfusion density

mean duration between Group B and C was statistically significant ($P = 0.048$). The common systemic comorbidity associated was hypertension. It was seen in one (4.5%) patient of Group A, 10 (41.6%) in Group B, and 14 (53.8%) in Group C patients. History of Ischemic heart disease was noted in one patient (3.8%) of Group B and 5 (19.2%) in Group C patients, suggesting high cardiovascular risk among diabetes patients with Group C. The late systemic complications like chronic kidney disease were seen in 2 (8.3%) patients among Group B and 4 (15.3%) patients in Group C.

The median LOGMAR visual acuity in the NPDR group was 0.31 ± 0.19 compared to 0.46 ± 0.24 in the PDR group. The *P* value there was significant between the above two groups (0.046). On further comparison of visual acuity among patients with or without DME, there was no statistically significant difference in both NPDR and PDR groups ($P = 0.68$) [Table 2a and b]. Incidence of macular edema more in NPDR group is 20 eyes (50%) compared PDR group i.e., 18 eyes (45%). Mean central macular thickness in the NPDR group is 360.63 ± 160.65 microns and 333.38 ± 105.23 microns in the PDR group, thus on comparison *P* value not significant (0.372). Among them, 8 (20%) eyes in NPDR and 7 (17.5%) eyes in the PDR group eyes had serous macular detachment (SMD). DME leads to moderated visual disturbance in both Groups B and C, but severe vision loss more with lesser incidence of DME due to macular ischemic changes in PDR group in 30% of eyes.

Vascular density is 19.65 ± 0.24 mm/mm^2 and perfusion density 36% ± 0.12%, both were altered with no diabetic retinopathy. In NPDR group the results we found were mean FAZ area 0.38 ± 0.16, perimeter 2.91 ± 0.58, circularity 0.59 ± 0.09 compared to PDR group FAZ area 0.48 ± 0.09 and perimeter 3.67 ± 0.82, circularity 0.53 ± 0.08 respectively. On analysis above results, we confirmed significantly altered parameters in PDR group compared to NPDR group. Vascular density mean value in NPDR group 18.89 ± 2.51 in comparison with PDR group 16.59 ± 1.96. The perfusion density mean value is 31.26 ± 7.03 in NPDR group and 23.19 ± 4.35 in PDR group. Thus even vascular density and perfusion density showed a statistically significant difference (0.0001) in different stages of diabetic retinopathy [Table 3].

Among eyes with DME NPDR, FAZ parameters mean area, Perimeter and Circularity were 0.41 ± 0.19 mm^2, 2.91 ± 0.59 and 0.61 ± 0.07 respectively while in PDR group Area 0.50 ± 0.09 mm^2, Perimeter 4.08 ± 1.03 and Circularity 0.51 ± 0.08, respectively. Quantitative parameters like vascular density and perfusion density in NPDR group 18.60 ± 2.43 and 31.08 ± 9.63 whereas in PDR group VD 16.11 ± 2.46 and PD 21.94 ± 4.62, respectively. Thus *P* value was significant in all parameters between the above two groups. Among the eyes with SMD, recorded mean values of FAZ metrics like area, perimeter and circularity were comparable between NPDR and PDR group. The vascular density and perfusion density in NPDR group with SMD eyes is 18.60 ± 2.43 and 31.08 ± 9.63. In PDR group VD 16.11 ± 2.46 and PD 21.94 ± 4.62 with SMD eyes [Table 4]. Thus we noted the significant change in vascular density and perfusion density.($P < 0.05$) in SMD eyes.

DISCUSSION

According to various population-based studies, the prevalence of DME among patients with type 1 diabetes was between 4.2% and 7.9%. On FAZ analysis, in group A, eyes with no diabetic retinopathy changes parameters FAZ area is 0.26 ± 0.1 mm^2, perimeter 2.20 ± 0.52 mm, circularity 0.82 ± 0.04 were comparable with normative data among nondiabetic eyes.[8] In patients with type 2 diabetes, it was between 1.4% and 12.8% of the Asian population.[9] We all know the diabetic macular maculopathy includes ischemic maculopathy along with diabetic macular edema. Current management of DME is based on l SD-OCT-based structural changes but we are not able to distinguish patients with ischemic maculopathy especially if the central retinal thickness is in the normal range.[10] So far the option of evaluating ischemic maculopathy was dependent on fundus fluorescein angiography as a gold standard imaging modality.[11] New imaging modality, OCTA angiography as an

Table 3: Logarithm of the minimum angle of resolution visual acuity, foveal avascular zone area, perimeter, circularity, vessel density, and perfusion density among Groups A, B, C (mean±standard deviation) and *P* value of comparison between group B and C

OCTA features	Group A (no DR)	Group B (NPDR)	Group C (PDR)	*P* (Group B vs. Group C)
Visual acuity (logmar)	0.16±0.06	0.32±0.19	0.46±0.24	0.046
FAZ (mm^2)	0.26±0.02	0.38±0.16	0.48±0.09	<0.01
Perimeter (mm)	2.20±0.21	2.91±0.58	3.67±0.82	<0.01
Circularity	0.82±0.04	0.59±0.09	0.53±0.08	<0.01
VD (mm/mm^2)	19.65±1.42	18.89±2.51	16.59±1.96	<0.01
PD (%)	36±2.06	31.26±7.03	23.19±4.35	<0.01

OCTA – Optical coherence tomography angiography, DR – Diabetic retinopathy, NPDR – Nonproliferative diabetic retinopathy, PDR – Proliferative diabetic retinopathy, FAZ – Foveal avascular zone, VD – Vessel density, PD – Perfusion density

Table 4: Comparison of vessel density and perfusion density changes (mean±standard deviation) in eyes with diabetic macular edema with serous macular detachment in Group B and Group C

Parameters with DME with SMD	NPDR (*n*=8)	PDR (*n*=7)	*P*
VD (mm/mm^2)	18.60±2.43	16.11±2.46	0.021
PD (%)	31.08±9.63	21.94±4.62	0.007

DME – Diabetic macular edema, SMD – Serous macular detachment, NPDR – Nonproliferative diabetic retinopathy, PDR – Proliferative diabetic retinopathy, VD – Vessel density, PD – Perfusion density

alternative noninvasive method of evaluating DME made a significant difference in managing diabetic maculopathy.[12] Yu *et al*. reported in their study that OCTA is comparable with that of FFA in assessing DMI.[13] The Early Treatment of Diabetic Retinopathy Study clearly mentions the importance of diagnosing macular ischemia as a predictive value for the progression of the disease.[14] Macular ischemic-associated FAZ changes and FAZ parameters measured by OCTA could also be used in the grading of diabetic retinopathy.[15] Many studies have proven ischemic maculopathy cases are usually refractory to either anti-VEGF or macular photocoagulation treatment.[15,16] Analysis of OCTA FAZ metrics will make a difference in our clinical practice by helping us uncover the eyes with macular ischemia without the need for invasive FFA.

FAZ parameters were quantified by measuring the area A, perimeter P, and circularity index C. In our study all FAZ parameters were within the normal range in eyes with no diabetic retinopathy, similar findings were noted in studies by Goudot *et al*.[17] Although in a study by Freiberg *et al*., stated similar results with predominant changes in superficial capillary plexus in comparison to our study, they reported early changes of FAZ were obvious in the deep capillary plexus.[18] When we compared the FAZ parameters between the eyes with no DR, eyes with NPDR, and eyes showing PDR, all the FAZ parameters showed a linear positive correlation with the stage of DR. FAZ parameters were normal in the eyes without DR while they were significantly altered in the eyes with PDR. The mean FAZ area of the SCP increased from 0.25 mm^2 in eyes without DR to up to 0.41 mm^2 in NPDR with DME and 0.50 mm^2 in cases with PDR with DME, eyes with DME showed larger FAZ area compared with eyes without DME. Our results are comparable to study by Dimitrova *et al*., study which reported a mean FAZ area of 0.51 mm^2 in PDR without DME and 0.58 mm^2 in cases with DME. A study by Lee *et al*. has also reported that the mean circularity index and mean FAZ area show a positive correlation with severity of DR.[19] The mean FAZ area size was also found to be inversely associated with visual function in the study by Freiberg *et al*., our results too showed a similar inverse correlation with respect to visual acuity.[18] Similarly, Arend *et al*.[20] reported a visual acuity score of 20/50 (0.4 in logmar) consistently in patients with DMI with a FAZ ≥0.55 mm^2, which is comparable with our findings PDR group of 0.4 with FAZ area >0.49 ± 0.09 mm^2.

When we compared FAZ metrics in eyes with or without DME, eyes with DME showed significantly deranged changes in FAZ metrics. On further subcategorizing eyes with DME cases into those with SMD and those without SMD in both NPDR and PDR groups we found no difference in visual acuity between the groups with or without SMD. Similar results were reported in a study by Hwang *et al*.[18] However, on the OCTA, FAZ metrics our data analysis revealed very interesting results. Among all FAZ metrics, only VD and PD were more affected in eyes with SMD while the FAZ area showed no change between the eyes with SMD and eyes without SMD. This finding may be due to the altered decreased vessel and perfusion density in eyes showing SMD, It is also reported by Hwang *et al*., that eyes showing SMD had significantly higher aqueous levels of vascular endothelial growth factor and pigment epithelial-derived factors.[21] These facts may indicate that ischemic retinal conditions are more in eyes with SMD and these eyes could be more prone for early progression of DR. This finding of using VD and PD on OCTA could be used in NPDR to predict higher risk of progression to develop PDR or worsening of PDR. These questions would be best answered by longitudinal studies in the future.

In our cross-sectional study, Quantitative analysis of parafoveal vessel density and perfusion density showed a correlation with the stage of diabetic retinopathy. A study by Schottenhamml reported that VD may predict DR severity with a relatively high sensitivity and specificity.[22] Durbin *et al*.[6] found that the mean perfusion density for the healthy group in the SRLs was 41, the mean vascular density was 22.5. In our study, we observed a PD of 36 and VD of 19.65 being reduced in diabetes patients' eyes with no evidence of diabetic retinopathy, Similar study reported by Dimitrova *et al*.[23] Dimitrova *et al*. also reported similar changes happening simultaneously in deep capillary layers.[23] However, according to the study by Al-Sheikh *et al*., alterations in vascular density in SCP correlated better with DR severity and their findings were comparable to our results in both NPDR and PDR groups.[24] Identifying eyes of diabetic patients that show lower vascular density in the macula on OCTA can potentially be useful to prognosticate the progression of retinopathy. This would alert the clinician that these patients are at risk of worsening of the DR and hence would require appropriate management of the systemic diabetic status by a multispecialty approach. The well-known factor is, 1-year risk of patients with DMI to develop progressive diabetic retinopathy was found to be almost 42%, which is significantly

higher than the individual without DMI.[14] Thus OCTA guides us in diagnosing DMI, which further helps in planning our follow-up and appropriate treatment for eyes at risk.

Limitations of our study

Our study was confined only to the analysis of superficial retinal plexus, due to limitations of software availability. The study involving analysis of the deep capillary plexus and the choriocapillaris will be more informative in understanding the microvascular changes in diabetic retinopathy. Choroidal thickness analysis is recent studies suggest a decreased choroidal perfusion in eyes with diabetic retinopathy. Choroidal thickness was not assessed in our study. Future studies trying to correlate Choroidal thickness with macular changes in diabetic retinopathy may help us to understand the pathogenesis in greater detail. Since the standard normative database of VD, PD, and FAZ values based on ethnicity is not available, it is difficult to compare various published studied, also same parameters being measured using different machines i.e. AngioVue and Cirrus HDOCT may not be comparable. The size of the study was not large enough to account for confounding factors such as glycemic control. Further large-scale studies with the study of various FAZ parameters in a longitudinal study with long-term follow-up are required to validate the correlations that are indicated in our cross-sectional study.

CONCLUSION

OCTA is a promising noninvasive tool to accurately assess the macular changes in various stages of diabetic retinopathy. It can reveal the underlying microvascular changes which helps in diagnosing ischemic maculopathy apart from diabetic macular edema. Thus FAZ parameters can be used as a biomarker for assessing various degrees of DME and DMI to help predict the progression of disease before its clinical manifestations. OCTA can be used to visualize and quantify the FAZ metric changes early and hence may help us for accurate disease severity and staging than what could be made out clinically. It also helps to prognosticate DR progression, vision, and assists in appropriate patient counseling along with informed treatment decisions. Serial quantitative measurements on OCTA are an added advantage that would avoid the potential risks of Fluorescein sodium dye injection in diabetic patients with end-stage complications. Thus OCTA is a useful noninvasive investigation tool in clinical settings, would certainly help in planning the follow-up, counseling, and choosing the appropriate treatment for eyes at risk.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Clinical profile of silicon oil-induced ocular hypertension: A prospective study

ABSTRACT

Background: Silicone oil (SO) is an important adjunct for internal tamponade, especially in eyes with proliferative vitreoretinopathy, diabetic tractional retinal detachments, and traumatic retinal detachments. SO has been associated with complications, such as cataract, keratopathy, and glaucoma. Secondary glaucoma has been reported to occur at any time in the postoperative period with a wide range of intraocular pressures (IOPs) and vision loss. **Aim:** The aim of this study is to assess the incidence and clinical profile of SO-induced ocular hypertension (SOIOH) at our institution, after pars plana vitrectomy (PPV) and silicone oil tamponade (SOT) in patient requiring the procedure. **Materials and Methods:** This is a prospective study of patients who attended Minto Ophthalmic Hospital, Regional Institute of Ophthalmology, Bengaluru from November 2017 to October 2020 who were requiring SOT for various vitreoretinal pathology. Preoperative complete ophthalmic evaluation was done, starting from visual acuity recording using Snellen's chart, slit-lamp examination, IOP measurement using Goldmann's applanation tonometry, gonioscopy, and dilated fundus examination. A standard three-port PPV with SO injection was performed. SOIOH was defined as IOP >21 mmHg after a period of 3 weeks postoperative, which required either medical or surgical therapy. Patients who developed SOIOH were compared to those who did not develop SOIOH (SOIOH free group), in terms of age, length of SOT, presence of retained SO in anterior chamber and angle, and IOP outcomes. **Results:** Among 26 patients who met our inclusion criteria were evaluated. Among them, 19 (73%) were male and 7 (27%) were female. The mean average age of all the patients was 36.88 (standard deviation [SD] 17.53) ranging from 10 years to 63 years. The mean average IOP of all patients preoperatively was 13.77 mm of hg (SD 3.45 mm of hg). It increased postoperatively showing a mean average postoperative IOP of all patients as 26.08 mm of hg (SD 11.2 mm of hg). The mean overall increase in IOP postoperatively was 12.31 mm of hg ($P = 0.001$). The mean average preoperative IOP was 12.2 mm of hg and mean postoperative IOP was 15.4 mm of hg in the SOIOH free group, with a mean average IOP spike postoperatively was 3.2 mm of hg ($P = 0.061$). In the SIOH group, the postoperatively average IOP spike was 15.75 mm Hg with values ranging from 14.75 mm hg preoperative to 30.5 mm hg postoperative ($P = 0.001$). **Interpretation and Conclusions:** Patients who underwent PPV with SOT should be followed up for longer period and those who have retained SO in anterior chamber or angles should be followed up more frequently as chances of development of SOIOH is more in them as proved by this study.

Keywords: Intraocular pressure, silicone oil-induced ocular hypertension, silicone oil tamponade

INTRODUCTION

In a wide variety of vitreoretinal procedures, silicone oil (SO) is an important adjunct for internal tamponade, especially in eyes with proliferative vitreoretinopathy, diabetic tractional retinal detachments, and traumatic retinal detachments. SO is a good internal tamponade with unique chemical characteristics such as an effective buoyant force and high surface tension.[1] There are currently two types of SO available to use in vitreoretinal surgery which differ in their viscosity. The 1000cs SO is less viscous and has a lower molecular weight, and the 5000cs SO is

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more viscous and has a higher molecular weight.[2] SO has been associated with complications, such as cataract, keratopathy, and glaucoma.[3-7] Secondary glaucoma has been reported to occur at any time in the postoperative period.[2] This secondary glaucoma can manifest with a wide range of intraocular pressures (IOPs) and vision loss.[2,3,8] Mechanisms of secondary glaucoma following the silicone oil tamponade (SOT) are, SO causing pupillary block, migration of SO into the anterior chamber with consequent mechanical obstruction to filtration, and emulsified SO causing mechanical obstruction to aqueous outflow.[2]

The purpose of our study was to assess the incidence and clinical profile of silicone oil-induced ocular hypertension (SOIOH) at our institution, after pars plana vitrectomy (PPV) and SOT in patient requiring the procedure due to various vitreoretinal pathologies.

MATERIALS AND METHODS

This is a prospective interventional study of patients who attended Minto Ophthalmic Hospital, Regional Institute of Ophthalmology, Bengaluru, from November 2017 to October 2020 who were requiring SOT for various vitreoretinal pathology. Twenty-nine patients were enrolled in the study. Preoperative complete ophthalmic evaluation was done, starting from visual acuity recording using Snellen's chart, slit-lamp examination, IOP measurement using Goldmann's applanation tonometry, gonioscopy, and dilated fundus examination. A standard three-port PPV with SO injection was performed. All had small fluid menisci to ensure the absence of overfill.

SOIOH was defined as IOP >21 mm hg after a period of 3 weeks postoperative, which required either medical or surgical therapy. Patients were analyzed in terms of age and length of SOT and those who developed SOIOH were compared to those who did not develop SOIOH (SOIOH free group), in terms of the presence of retained SO in anterior chamber and angle, and IOP outcomes and development of glaucomatous cupping in the form of increase in the cup to disc ratio during their follow-up visits which was every three monthly.

Exclusion criteria were patients previously diagnosed with glaucoma, ocular hypertension, glaucoma suspects, and those on IOP-lowering agents. Furthermore, patients with SO overfill or IOP spikes on the postoperative days 1–21 were excluded from the study.

Statistical analysis

The data obtained from the patients were recorded and analyzed. Descriptive analysis of the population's characteristics was carried out. Results of continuous variables are reported as mean and standard deviation (SD). The differences between quantitative variables were analyzed using paired *t*-test. $P < 0.05$ was considered as statistically significant for all the comparisons.

Data were analyzed using SPSS 20.0 is an IBM software Version and Microsoft Excel 2013.

The sample size was calculated using single mean-paired *t*-test

$$N_{pairs} = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)}{\Delta^2} + \frac{z^2_{1-\alpha/2}}{2}$$

where $\mu 1$ = Pretest mean

$\mu 2$ = Posttest mean

$\sigma 1$ = SD in the pretest

$\sigma 2$ = SD in the posttest

Δ = Effect size

α = Significance level

$1-\beta$ = Power

Taking alpha error as 1.96 and absolute precision at 10%, the minimum sample size using the above formula was 20.

RESULTS

Among 29 patients enrolled in the study, three subjects were excluded later because of immediate postoperative IOP spikes within 3 weeks. Hence, 26 patients who met our inclusion criteria were evaluated. Among them, 19 (73%) were male and 7 (27%) were female. The mean average age of all the patients was 36.88 (SD 17.53) ranging from 10 years to 63 years. The average length of SOT was 17.5 months (2–36 months).

Of these 26 patients, SOT was done for different reasons such as 7 (30%) cases had proliferative diabetic retinopathy with tractional retinal detachment, 11 (42%) had traumatic retinal detachment, 4 (15%) with rhegmatogenous retinal detachment, and rest of the 4 (15%) patients with aphakic retinal detachment.

The mean average IOP of all patients preoperatively was 13.77 mm of Hg (SD 3.45 mm of Hg). It increased postoperatively showing a mean average postoperative IOP

of all patients as 26.08 mm of hg (SD 11.2 mm of hg). The mean overall increase in IOP postoperatively was 12.31 mm of hg ($P = 0.001$)

Among 26 patients evaluated, 16 who had persistently raised IOP after 3 weeks were included in the SOIOH group and ten patients maintained normal range of IOP and were included in SOIOH free group. The mean average preoperative and postoperative IOPs in both groups are given in Table 1. The average rise in IOP in the SOIOH group was 15.75 mm hg ($P = 0.001$) and in SOIOH free group was 3.2 mm hg ($P = 0.061$). Comparison between preoperative and postoperative IOP among the patients showed statistically significant ($P < 0.001$) increase after SOT.

Sixteen patients who had persistently raised IOP were put on medical treatment and followed up frequently[7] of the SOIOH group who were not responding to medical treatment underwent SO removal and three of them underwent filtering surgery.

Three out of 10 (30%) patients in SOIOH free group and 13 out of 16 (81%) patients in SOIOH group had emulsified SO in the anterior chamber, which was statistically significant with $P = 0.009$ [Figures 1,2 and Tables 2,3] and visible oil in superior angle on gonioscopy. Two out of 10 (20%) patients in SOIOH free group and 10 out of 16 (62.5%) patients in the SOIOH group showed glaucomatous optic disc cupping.

DISCUSSION

The mechanisms of IOP elevation following SOT are directly attributed to pupillary block caused by SO and emulsified SO in the anterior chamber. Histological studies have shown obstruction of trabecular meshwork by silicone bubbles, pigmented cells, and silicone-laden macrophages.[9]

According to a study by Ichhpujani *et al*.,[2] the reported frequencies with which SOT is associated with postoperative IOP spike can vary widely, ranging from 2% to 50% and another study by Nariani *et al*.[10] where they used SOT with 1000cs SO after PPV seemed to be associated with the development of SOIOH in 33.3% of patients. Our study showed SOIOH for 61% of patients enrolled in our study. This discrepancy may be related to the underlying disease of the eye, which can alter aqueous outflow and inflow and the resultant IOP represents the balance between the two.

The length of SOT was associated with increased incidence of SOIOH. This suggests that SO should be removed as soon as there is no further need for it. However, even after SO removal the majority of patients with SOIOH had persistence of the disease. This attributes that the pathogenesis of SOIOH includes irreversible damage to the angle structures. And also small silicone bubbles could have persisted in the trabecular meshwork, even after oil removal.

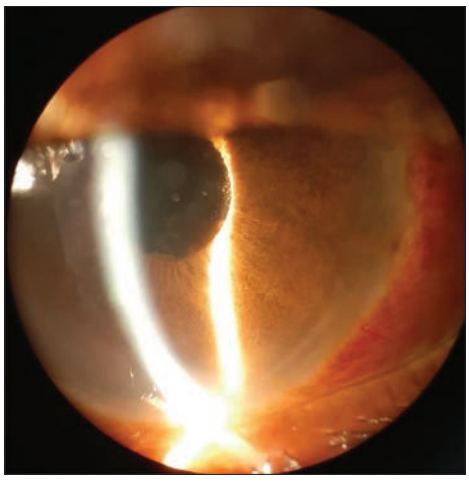


Figure 1: Emulsified silicone oil deposited on iris and intraocular lens

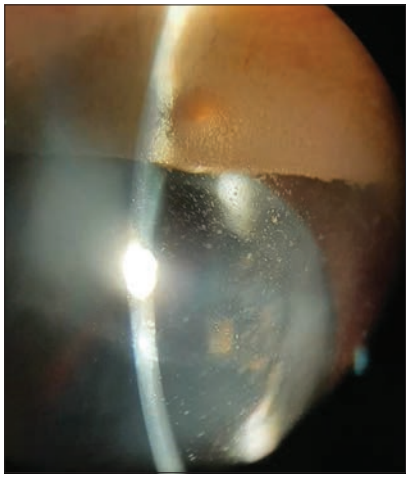


Figure 2: Emulsified silicone oil in the anterior chamber causing inverse hypopyon

Table 1: Comparison of intraocular pressure pre- and post-operative in silicone oil-induced ocular hypertension and silicone oil-induced ocular hypertension free group

	Mean average preoperative IOP	Mean average postoperative IOP	Mean IOP spike	*P*	Duration of SOT (months)
SOIOH (n=16)	14.75±3.4	30.5±8.8	15.75	0.001*	20 (3-35)
SOIOH free group (n=10)	12.2±2.8	15.4±3.6	3.2	0.061	12 (2-35)

*p value<0.05 was considered significant. SOIOH – Silicone oil-induced ocular hypertension, IOP – Intraocular pressure, SOT – Silicone oil tamponade

Table 2: Clinical characteristics of patients with SOIOH and SOIOH free group

	Retained SO in anterior chamber or angle, *n* (%)	Glaucomatous optic disc cupping, *n* (%)
SOIOH (*n*=16)	13 (81)	10 (62.5)
SOIOH free group (*n*=10)	3 (10)	2 (20)

SOIOH – Silicone oil-induced ocular hypertension, SO – Silicone oil

Table 3: Comparison of anterior chamber findings in both groups

	Retained SO in the anterior chamber		Total	Pearson χ^2, *P*
	Present	Absent		
SOIOH	13	3	16	6.829, 0.009
SOIOH free group	3	7	10	
Total	16	10	26	

SO – Silicone oil, SOIOH – Silicone oil-induced ocular hypertension

In our study, we found that emulsified SO in the anterior chamber was more common in the SOIOH group (81%) as compared to the other group (30%). This is in accordance with other studies by Valone and McCarthy.[11] and Nariani *et al*.[10] where they showed increased incidence in ocular hypertension in eyes with retained SO in the anterior chamber. The absence of raised IOP in few eyes with retained SO in the anterior chamber or angles can be due to the pressure-lowering effect of ciliary body detachment by cyclitic membranes or total retinal detachments. Fibrous tissue has been shown to form around silicone vesicles, the retraction of these may lead to these detachments.[12]

We excluded patients with immediate IOP spike to investigate a more homogeneous group of patients who had no spikes of IOP in the first 3 weeks of postoperative days and patients without SO overfill. SO overfill can lead to acute glaucoma with shallowing of the anterior chamber and oil displacement into the anterior chamber.

de Corral *et al*. have shown that IOP elevation associated with SO injection is independent of systemic conditions such as diabetes mellitus.[13]

In the study by Nariani *et al*.,[10] age and family history of glaucoma had a positive correlation with the development of SOIOH. This is consistent with the tendency of glaucoma to be an age-related disease. In our study, we failed to analyze any correlation of age with the development of SOIOH and any correlation of family history of glaucoma or systemic conditions with SOIOH.

Weinberg *et al*.[14] reported elevated IOP after PPV alone, without SOT attributing it to neovascularization, hemorrhage, hemolysis, or phacolysis.[14] IOP elevation also may be due to peripheral anterior synechiae and/or inflammation. One of the major drawbacks of our study was the presence of certain confounding factors. Raised IOP could not be attributed completely to SOT alone in all cases. Steroid-induced glaucoma and postoperative inflammatory glaucomas could also have been contributory factors.

IOP elevation is a common occurrence after intravitreal SO injection used in the management of complicated retinal cases. The underlying mechanism is often unclear, and may frequently be multifactorial in nature.[15] Patients should be monitored closely for the development of elevated postoperative IOP, especially if they have a history of elevated preoperative IOP, and they may benefit from aggressive medical and or surgical treatment of glaucoma with SO removal, glaucoma implants, or cyclodestructive procedures to avoid additional optic nerve damage.

Limitations

Our study was limited by its relatively small number of patients. Moreover, we failed to include visual field and pachymetry testing to define the SOIOH group with more accuracy.

CONCLUSIONS

Ocular hypertension following intravitreal injection of SO is a known complication. So patients who underwent PPV with SOT should be followed up for the longer period and in those who have retained SO in the anterior chamber or angles should be followed up more frequently as chances of development of SOIOH are more in them as proved by this study. The longer the duration of tamponade caused by SO, the more is the incidence of SOIOH. Hence, it is advisable to remove SO as soon as its purpose has been served.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Comparative study of intracameral lidocaine and topical mydriatics in pupil dilation during phacoemulsification

ABSTRACT

Introduction: Intracameral injection of preservative-free lidocaine is used as an alternative to reduce the potential disadvantages of common mydriatics in cataract surgery. **Aims and Objectives:** The aim is to evaluate pupil dilation by an intracameral injection of lidocaine during phacoemulsification cataract surgery and compare the results with those using conventional topical mydriatics. **Methods:** A prospective cohort study was conducted in 60 consecutive patients undergoing phacoemulsification cataract surgery under topical anesthesia at Government Medical College, Kannur from July 2018 to December 2019. Patients were allocated to intracameral lidocaine or topical mydriatics for dilation of the pupil before phacoemulsification. **Results:** The preoperative pupil size was similar in intracameral lidocaine (2.90 ± 0.3 mm) and topical mydriatic (2.81 ± 0.4 mm) groups. Pupil dilation was slightly more in the topical mydriatic group (7.31 ± 1.0 mm) compared to the intracameral lidocaine group (6.96 ± 1.0 mm). The pupil size at the end of the surgery was nearly similar in both groups. Mean duration of the surgery was similar in both the groups. Both the groups had 27 patients who maintained dilation till the end of the surgery. The difference between the groups was not statistically significant and a *post hoc* power analysis showed the need for studies with a larger sample size. **Conclusion:** This study shows that injection of 0.2–0.3 ml of preservative-free lidocaine 1% intracamerally provides persistent, stable, satisfactory pupil dilation comparable to that of topical mydriatics, for safe phacoemulsification, and intraocular lens implantation. However, studies with a larger sample size are needed to confirm that both interventions perform similarly.

Keywords: Intracameral, lidocaine, mydriatic, pupil size

INTRODUCTION

Inadequate pupil dilation increases the risk of intraoperative complications in cataract surgery. Topical administration of anticholinergic or sympathomimetic agents are used to achieve pupil dilation for cataract surgery. However, there are several disadvantages with the use of topical eye drops for pupillary dilation. Topical eyedrops have slow and poor penetration through the cornea, which delays the onset of pupil dilation and lead to an increased waiting time before cataract surgery.[1,2] Physiological and anatomic barriers result in absorption of < 1% of the instilled mydriatic agents through the cornea and low bioavailability in the anterior chamber.[3-5] The higher concentration of topical mydriatics needed to achieve adequate mydriasis may rarely cause systemic toxicity such as acute pulmonary edema and hypertensive crisis. Systemic toxicity is common in children and high-risk patients with uncontrolled hypertension or poor cardiac function.[6-8] The effects of topical mydriatics may not sustain for the duration of surgery[9] and lead to pupil constriction, especially in patients with intraoperative floppy iris syndrome[10] and diabetes mellitus.[11]

Intracameral injection of preservative-free lidocaine was attempted as an alternative to reduce the potential

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disadvantages of common mydriatics.[12] Since anesthetic agents lack adrenergic or anticholinergic properties, these mydriatic and cycloplegic effects of intracameral lidocaine is due to a paralytic effect on the iris.[13]

Cataract surgery is the most common ophthalmic surgical procedure performed in India. We designed a prospective study to compare pupil dilation and operative outcomes of conventional topical mydriatics and intracameral injection of lidocaine in persons undergoing cataract surgery by phacoemulsification at a tertiary care teaching eye care hospital in north Kerala.

METHODS

The study protocol that used a prospective cohort design was approved by the institutional review board and ethics committee. Informed consent was obtained from all participants prior to enrolment in the study. The study was conducted from July 2018 to December 2019 at the Ophthalmology Department of the study institute. Patients with age-related cataract posted for cataract surgery, willing to follow the study protocol and provided informed consent were enrolled. Patients with ocular surface disorders, on immune suppressive therapy, diagnosed with collagen vascular diseases, previous refractive ocular surgeries and on chronic topical medications for any ocular condition, and diabetes mellitus were excluded from the study. Consecutive subjects were enrolled for the study after confirming eligibility.

Each subject had a detailed preoperative assessment that included uncorrected and best-corrected visual acuity, intraocular pressure and anterior chamber depth assessments, slit-lamp biomicroscopy assessment of the cornea and anterior segment, and posterior segment assessment. The lens was graded based on the LOCS III grading system. The operating surgeon allocated patients to one of the two intervention groups using a nonrandomized sequential alternate allocation approach. Masking of the operating surgeon was not possible as one of the intervention arms was the use of intracameral medication.

Intracameral lidocaine or topical mydriatics was used to dilate the pupil before cataract surgery by phacoemulsification and intraocular lens implantation. The topical mydriatic group received 1 drop of tropicacyl plus (tropicamide 0.8% and phenylephrine hydrochloride 5%) four times at 15 min interval in the Ophthalmology OutPatient Department starting 60 min before surgery. The intracameral lidocaine group was given preservative-free lidocaine 1% (0.2–0.3 mL) intracamerally after entry into the anterior chamber on the operating table. Epinephrine was not added to the irrigating solution. In both groups, the horizontal pupil diameter was measured before pupil dilation, after dilatation and at the end of surgery using the same caliper and by the same operator (LNV). All patients underwent cataract surgery by phacoemulsification by the same surgeon (LNV). The total surgical time and need for an additional mydriatic agent during the procedure were recorded.

The sample size for the study was estimated based on the estimates reported by Nikeghbali *et al*.[12] The sample size for the study was estimated as 2 based on the reported standard deviations of 0.09 and 0.08 in the two groups and reported mean difference of 0.46 reported by Nikeghbali *et al*., 5% significance and 80% power. As the derived sample size was small, we decided to perform an observational study based on a convenience sample size of 30 to derive estimates from the local population that can be used to design the study.

The data were entered into an MS Excel spreadsheet and subsequently exported to SPSS software (IBM SPSS Statistics for Windows, v 22.0, Armonk, NY; IBM Corp) for statistical analysis. An independent *t*-test was used to compare the means of continuous variables and a Chi-square test was used to compare categorical variables. A $P < 0.05$ was considered statistically significant.

RESULTS

The study included 30 patients in each group. The two groups did not differ by preoperative pupillary size and was 2.90 ± 0.3 mm in intracameral group and 2.81 ± 0.4 mm in topical mydriatic group [Table 1]. The distribution of preoperative visual acuity and IOP was similar in both the groups. The LOCS III classification showed that NO2-NO3+ variable amount of cortical cataract and posterior subcapsular cataract stage was the predominant type of cataract operated in both the groups.

The pupil dilated slightly more in the topical mydriatic group 7.31 ± 1.0 mm compared to the intracameral lidocaine group 6.96 ± 1.0 mm although this difference was not statistically significant [Table 1]. The pupil size at the end of the surgery were almost similar but slightly more for topical group (6.73 ± 1.0 mm) compared to intracameral lidocaine group (6.51 ± 1.4 mm) although the difference was not statistically significant [Table 1]. The mean difference, or in other words average change in pupil size was +4.5 mm in topical mydriatic group and +4.06 mm in intracameral lidocaine group. Thereafter, pupil size changed to −0.58 in topical mydriatic group and −0.45 mm in intracameral lidocaine group.

The duration of the surgery was same in both the groups 12.93 ± 1.23 min in intracameral lidocaine group and 12.90 ± 1.26 min in topical mydriatic group [Table 2]. Both groups had 27 patients who maintained dilation until the end of the surgery and 3 patients who didn't maintain dilation. Additional mydriatic was used in 1 patient in intracameral lidocaine group compared to 2 patients in topical mydriatic group. Intraoperative complications were seen among 2 patients in intracameral lidocaine group and 2 patients in topical mydriatic group. There were no postoperative complications in any patients. These differences did not show any statistical significance [Table 2]. Postoperative striate keratopathy was present in the first 2 patients in intracameral lidocaine group and was solved by injecting air bubble into anterior chamber before injecting preservative free lidocaine intracamerally for subsequent surgeries.

DISCUSSION

Topical mydriatic agents have been routinely used to dilate pupils preoperatively in cataract surgery. It is commonly achieved by topical administration of anticholinergic (passive) and sympathomimetic (active) mydriatic agents. This regimen has many drawbacks. Slow penetration through cornea delays onset of mydriasis. Thus, the waiting time to operate is longer than the total operating time. There is limited bioavailability of topically administered substances and there is significant systemic absorption which leads to risk of cardiovascular side-effects, especially in patients with hypertension, cardiovascular diseases and in children. Another disadvantage is that mydriatic effect tends to wear off during surgery. The use of benzalkonium chloride as a preservative in topical eyedrops has led to side effects, mainly on the cornea (e.g., punctate epithelial erosion causing poor intraoperative surgical view). Therefore, alternative methods of pupil dilation have been assessed with the goal of decreasing the risk for unwanted local and systemic side effects.

The baseline characteristics of the study population in this study was consistent with previously reported studies.[14-17] The changes in pupil size in our study is consistent with previous studies[15-17] comparing the effectiveness of topical mydriatics with that of intracameral lidocaine 1.0% alone or intracameral lidocaine 1.0% in combination with other mydriatic agents

Table 1: Pupil size changes in the study population

Pupil size in millimetre	Mean±SD		Independent sample *t*-test (*P*)	Mean difference	
	Intracameral lidocaine, (*n*=30)	Topical mydriatic, (*n*=30)			
Pupil size before dilation	2.90±0.3	2.81±0.4	0.337	Initial pupil size	Initial pupil size
Pupil size after dilation	6.96±1.0	7.31±1.0	0.295	4.06	4.5
Pupil size at the end of surgery	6.51±1.4	6.73±1.0	0.578	−0.45	−0.58

SD – Standard deviation

Table 2: Intra- and post-operative findings in the two groups

Surgery findings	Intracameral lidocaine (*n*=30), *n* (%)	Topical mydriatic (*n*=30), *n* (%)	Chi-square test (*P*)
Duration of surgery (*n*=60)			
Duration in minutes (mean±SD)	12.93±1.23	12.90±1.26	0.877
If pupil dilation maintained till the end (*n*=60)			
Yes	27 (90.0)	27 (90.0)	1.000
No	3 (10.0)	3 (10.0)	
Additional mydriatic used (*n*=60)			
Yes	1 (03.3)	2 (06.7)	0.554
No	29 (96.7)	28 (93.3)	
Intraoperative complications (*n*=60)			
Yes	2 (06.7)	2 (06.7)	1.000
No	28 (93.3)	28 (93.3)	
Postoperative complications (*n*=60)			
Yes	0	0	1.000
No	30 (100)	30 (100)	
Postoperative striate keratopathy (*n*=60)			
Yes	2 (06.7)	0	0.789
No	28 (93.3)	30 (100)	

SD – Standard deviation

such as cyclopentolate 0.1% and phenylephrine 1.5%. These studies found that the use intracameral mydriatics alone produced prompt pupil dilation intraoperatively without the previous use of topical mydriatics. However, we found that the difference in pupil dilation or duration of surgery or time to dilation between intracameral and topical mydriatics was not statistically significant in this series.

Previous studies[12,16,17] have reported that intracameral mydriatics produced adequate pupil dilation during cataract surgery. The potential advantages of intracameral mydriatics are multiple. First, omission of preoperative dilating eyedrops will ease the burden on the hospital staff. Moreover, the use of intracameral mydriatics in cataract surgery prevents the corneal side effects of intensive preoperative mydriatic agents. In addition, surgery can be scheduled using a staggered system to reduce the waiting time for patients. A study by Cionni *et al*.[13] found that intracameral lidocaine 1.0% was effective in attaining good pupil dilation without the use of topical mydriatics preoperatively. The mydriatic effect of intracameral mydriatics did not wear off during the surgery, and the pupils were further dilated at the end of surgery. Sodhi PK *et al*.[17] evaluated the use of intracameral lidocaine 1.0% to dilate the pupil in glaucoma filtering surgery intraoperatively and showed that intracameral lidocaine 1.0% can be used as a dilating agent in undilated eyes. A study by Nikeghbali *et al*.[18] found that both intracameral lidocaine 1.0% and topical groups (cyclopentolate 1.0% and phenylephrine 5.0%) achieved significant pupil dilation in cataract surgery.

The sustenance of pupil dilation, use of additional mydriatics, and intraoperative complications were similar for both groups and consistent with previous reports.[9,16-18] In our study, the amount of pupil dilation was not significantly different during surgery, which lasted approximately 12 min. However, it is not clear how long the pupil dilation lasts after an intracameral lidocaine injection. We found pupil dilation in both the topical group and intracameral group to be similar as opposed to previous studies that reported a significant difference in pupil dilation between intracameral and topical mydriatics.[12-18] It is possible that the lack of difference maybe a true population difference based on the characteristics of the iris. However, a *post hoc* power analysis showed that we did not have enough power (10.32%) to determine if this is a true lack of difference. A repeat estimation of the sample size based on the results of our study indicated the need for a much larger study to support the hypothesis that intracameral mydriatics have greater effectiveness than topical mydriatics in our population.

The current study highlights the importance of an appropriate sample size estimation and an understanding of the underlying assumptions that are used to determine sample size. The estimated sample size of 2, based on the previous study results, suggests an exceptionally large difference between the two interventions. Such a large difference between the interventions will make it unethical to withhold the better performing intervention, in this case, intracameral mydriatics to all patients. However, in clinical practice, we did not see such a huge difference between the two interventions. We decided to do an observational study as a cohort design before designing a randomized clinical trial to get better estimates of the sample size that may be needed for an adequate power (at least 80% power). The sample size, based on our initial results, was estimated as a minimum of 380 subjects if we design a noninferiority, randomized clinical trial.

Estimates of sample size are based on clinical assumptions and it is important to examine the underlying assumptions used. Sample size estimates for interventions are best derived from previous meta-analyses or clinical trials. In the absence of such studies, a prior study with a cohort design or a cross sectional study may be used. A pilot study is preferable if there are no prior estimates in the literature or if the estimated sample size seems implausible based on clinical experience.

CONCLUSION

Although our study shows that intracameral preservative free lidocaine provides persistent, stable, satisfactory pupil dilation , we recommend future studies from diverse settings to better understand the comparative effectiveness of intracameral mydriatics in our population and using a randomized clinical trial design. We recommend further studies from diverse settings to better understand the comparative effectiveness of intracameral mydriatics in our population and using a randomized clinical trial design.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Decision making in pterygium surgery: Our experience noting the length of pterygium

ABSTRACT

Background: This is a prospective study which aims: To compare the preoperative and postoperative corneal astigmatism in patients undergoing pterygium excision by conjunctival autograft technique using autologous blood. To determine the correlation of pterygium length with preoperative and postoperative corneal astigmatism and thus ascertain an early indication for pterygium surgery. **Materials and methods:** 75 patients with primary pterygia were evaluated after dividing them into three groups based on length, Grade A - < 2mm, Grade B - 2 – 4mm and Grade C - > 4mm. Preoperative and postoperative corneal astigmatism were compared between the three groups using autorefraction and keratometer readings. Postoperative astigmatism was recorded on three visits – day 7, day 28 and third month. **Statistical analysis:** Statistical Package for Social Sciences (SPSS) version 19.0 for windows was used. Spearman's rank order (ρ) was calculated to observe correlation of pterygium length with the preoperative and postoperative corneal astigmatism. A p-value < 0.05 was considered statistically significant. **Results:** The mean length of the pterygium was 2.77 ± 0.12mm. Majority had with – the – rule astigmatism (64%). Postoperatively mean uncorrected visual acuity (UCVA) increased significantly from 0.533 ± 0.03 to 0.78 ± 0.03 ($P < 0.0001$). Preoperative mean keratometric astigmatism of 2.55 ± 0.36D significantly decreased to 1.213 ± 0.20D postoperatively ($r = 0.89$, $P < 0.0001$). A positive correlation between the length of pterygium and both preoperative ($\rho = 0.68$, $P < 0.001$) and postoperative ($\rho = 0.53$, $P < 0.001$) corneal astigmatism was observed. **Conclusion:** The increase in the length of pterygium significantly correlated with the degree of preoperative corneal astigmatism. The evidence of significant improvement in visual acuity and decrease in pterygium induced corneal astigmatism was observed three months postoperatively by conjunctival autograft technique with autologous blood. Hence, pterygium induced corneal astigmatism of length > 2mm is an early indication for surgical intervention.

Keywords: Conjunctival autograft, corneal astigmatism, keratometry, pterygium

INTRODUCTION

Pterygium is a degenerative and hyperplastic process in which bulbar conjunctiva actively invades the cornea.[1] Clinically pterygium appears as a wing-shaped, vascular, and fleshy growth of conjunctiva encroaching onto the cornea on either side within the palpebral fissure.

Epidemiological studies worldwide have shown that the prevalence rates of pterygium range from 0.3%–37.46%. Pterygium is a very common degenerative condition seen in the Indian subcontinent with a prevalence of 5.2%. Pterygia cause corneal distortion and induce a significant amount of astigmatism which has been previously measured in various studies by refraction and keratometry.[2,3] This astigmatism may occur either due to pooling of tears ahead of the pterygium or by traction generated by the pterygium mechanically pulling on and distorting the cornea in the horizontal meridian.[4] The induced astigmatism (with-the-rule astigmatism) may become significant to cause visual distortion or dimness, even when

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the pterygium remains distant from the visual axis. Pterygia are more commonly seen in tropical climates and most of them develop on the nasal limbus thus implicating direct sunlight and ultraviolet radiation as aggravating factors.[5-7]

Pterygium excision surgeries using amniotic membrane graft and conjunctival autograft are better surgical techniques than bare sclera as far as reducing astigmatism is concerned.[8] Although its effect on corneal curvature and visual acuity has been recognized and many surgical techniques described for the same, not much attention has been given to the relief of astigmatism by early surgical treatment. Although many studies have correlated the size of pterygium with preoperative astigmatism, only few have attempted to determine the influence of the pterygium length on postoperative corneal astigmatism with conjunctival autograft technique without suture and glue.

In the present study, an attempt is made to determine the correlation between length of the pterygium on preoperative as well as postoperative astigmatism with conjunctival autograft technique, and to know whether corneal astigmatism is an early indication for surgical intervention. Kampitak suggests that a pterygium exceeding 2.25 mm of length should be considered within the limits of surgery.[9] On the contrary, Oner *et al*. recommended that pterygia whose length exceeds 3 mm should be considered within the limits of surgery.[10]

Aims and objectives

1. To compare the preoperative and postoperative corneal astigmatism in patients undergoing pterygium excision
2. To determine the correlation between length of pterygium on preoperative and postoperative astigmatism
3. To know whether corneal astigmatism is an early indication for surgical intervention.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Ophthalmology Department of a tertiary care hospital. Seventy-five eyes of 75 patients with primary pterygium were included in this study. The duration of study was 1 year. This study was approved by the institutional review board.

Inclusion criteria

Patients aged 25–65 years with primary nasal pterygium:

1. Consenting for surgery
2. With constant irritation
3. For cosmetic reasons
4. Encroaching the visual axis inducing visually significant astigmatism.

Exclusion criteria

1. Pseudopterygium, recurrent pterygium
2. Postoperative graft dislocation
3. Cataract
4. Glaucoma
5. Corneal opacity
6. Macular degeneration
7. History of trauma to the eye
8. Previous surgical intervention to the eye.

Sample size

The prevalence of pterygium in India is estimated to be 5.2% considering 95% confidence interval and 5% permissible error, sample size was calculated to be 75 cases.

A written informed consent was obtained from all patients. After obtaining ocular and systemic history, ocular examination was done which included Snellen's uncorrected visual acuity (UCVA) (in decimal), objective refraction, keratometry, and slit-lamp examination. The length of the pterygium was measured using the Haag-Streit slit-lamp biomicroscope by projecting a horizontal slit beam from the limbus to the apex of the pterygium and recording the length in millimeters, and the cases were divided into three groups:[11]

- Group A – <2 mm
- Group B – 2–4 mm and
- Group C – above 4.0 mm.

Manual keratometry (Bausch and Lomb) and objective refraction with Canon Auto-refractokeratometer were done in all patients.

All surgeries were performed by the same surgeon and a free conjunctival autograft was placed with no glue and no suture technique in all cases. Under local anesthesia, the pterygium head was dissected from its corneal edge till the limbus, separated with blunt dissection from the underlying sclera and overlying bulbar conjunctiva till the insertion of the medial rectus muscle. Then, the pterygium was excised along with its accompanying tenon's fascia. The bare sclera defect was measured with calipers and a free limbal conjunctival graft was harvested from the superotemporal conjunctiva of the same eye and placed on the bare sclera with no sutures or glue. Adherence of the graft was achieved through natural hemostasis. Ciprofloxacin with dexamethasone ointment was applied and the eye was padded.

The eye pad was removed on the first postoperative day and the graft was checked for its adherence. Ciprofloxacin with dexamethasone eye drops four times daily was prescribed for 4 weeks and tapered weekly. All the patients were

followed – up on day 7, 1st month–3rd month. Keratometric data, refraction, and UCVA (in decimal) were obtained on all the follow-ups.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 19.0 for windows (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. IBM Corp. Released 2011). Descriptive statistics were used to describe the clinic-demographic data. Preoperative and 3rd month postoperative astigmatism by keratometry were compared using the paired *t*-test. Alpins astigmatism analysis was used to calculate target-induced astigmatism (TIA) and difference vectors (DVs).[12] Spearman's rank order (ρ) was calculated to observe correlation of pterygium size with the preoperative and postoperative corneal astigmatism. A $P < 0.05$ was considered statistically significant.

RESULTS

The 75 eyes of 75 patients selected were divided into three groups based on the length of pterygium. Most of the patients (27%) belonged to the age group of 46–65 years with a mean age of 47 ± 12 years. Females constituted 75% of cases while 25% of cases were males. The prevalence of pterygium was found to be more among the agriculturists (54%), followed by laborer's (29%); both belong to the outdoor occupation group.

The length of the pterygium varied between 1.25 mm and 6 mm and the mean length was 2.76 ± 0.12 mm. All eyes had nasal primary pterygia of which Group A had 12 eyes (13%), Group B had 52 eyes (71%), and Group C – 11 eyes (16%), respectively.

It was observed that Group A had an improvement in UCVA of one line after surgery ($P < 0.05$). In Group B, the preoperative mean UCVA of 0.52 ± 0.06 improved to 0.798 ± 0.06 ($P < 0.0001$) postoperatively, which corresponds to 1–2 lines of Snellen's visual acuity. Group C showed a preoperative UCVA of 0.33 ± 0.14 which significantly improved to 0.57 ± 0.18 ($P < 0.0001$) postoperatively (3rd month), indicating 2–3 lines improvement in Snellen's visual acuity [Table 1]. Preoperative analysis of pterygium showed that 64% (48 cases) had with-the-rule astigmatism, 20% (15 cases) had oblique astigmatism, and 16% (12 cases) had against-the-rule astigmatism.

The mean preoperative corneal astigmatism of the study group using keratometry was 2.55 ± 0.364 D which significantly

Table 1: Comparison of Pre and Postoperative Uncorrected visual acuity (in Decimal) in relation to pterygium size

Group	Length of Pterygium (mm)	Uncorrected Visual Acuity (UCVA) (mean±SD)		Improvement in Snellen's	*P*
		Preoperative	Postoperative (3rd month)		
A	<2 mm	0.7666±0.080	0.875±0.0445	1 line	<0.05
B	2-4 mm	0.5221±0.0300	0.7980±0.0280	1 to 2 lines	<0.0001
C	> 4 mm	0.3318±0.0626	0.572±0.0810	2 to 3 lines	<0.0001

Table 2: Comparison of Pre and Post - operative Corneal Astigmatism (in Diopter) with the Grade of Pterygium

Group	Preoperative Keratometric astigmatism	Postoperative Keratometric astigmatism	Reduction (mean±SD)	Paired *t* - test	Pearson's correlation (*r*)	*P*
A	1±0.213 D	0.4791±0.0782D	0.4791±0.1582D	3.17	0.74	<0.05
B	2.197±0.353D	0.9182±0.128D	1.283±0.2504D	5.1	0.86	<0.0001
C	5.909±1.483D	3.409±1.0608D	2.5±0.579D	4.31	0.95	<0.001

Table 3: Refractive astigmatism as measured by autorefractometer

Group	Preoperative astigmatism (mean±SD)	Postoperative astigmatism (mean±SD)	Reduction (mean±SD)	Paired *t* - test	Pearson's correlation (*r*)	*P*
A	1.0416±0.197	0.5±0.075	0.542±0.159	3.398	0.64	<0.05
B	2.381±0.3350	0.903±0.1292	1.490±0.265	5.540	0.67	<0.0001
C	6.204±0.9455	2.272±0.6100	3.931±0.617	6.362	0.77	<0.0001

Table 4: Correlation between pterygium length and preoperative and postoperative corneal astigmatism (*n*=75)

Pterygium length (mm)	Preoperative corneal astigmatism	Postoperative corneal astigmatism (3 months)	Spearman's rank order (ρ) - Preoperative	Spearman's rank order (ρ) - Postoperative	*P*
2.76±0.12	2.55±0.364	1.21±0.2044	0.680	0.53	0

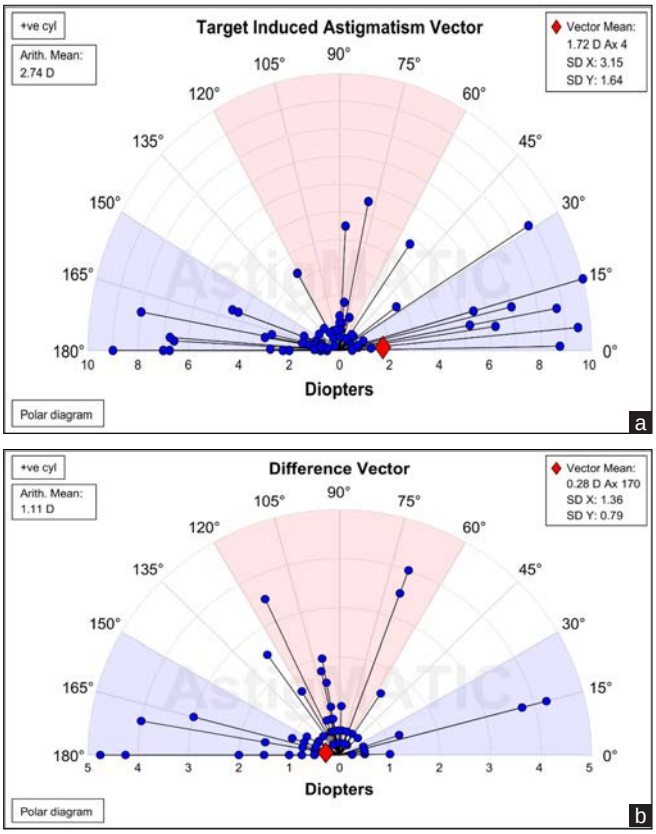


Figure 1: Alpins single-angle plots for the total study population (n=75 eyes). Target-induced astigmatism (TIA, a) and difference vector (DV, b) arithmetic and vector means are shown. Images generated by AstigMATIC Software

reduced to 1.21 ± 0.204 D ($P < 0.0001$) 3 months after surgery. The mean preoperative astigmatism was 1 ± 0.213 D, 2.197 ± 0.353 D, and 5.9 ± 1.483 D in Groups A, B, and C, respectively which indicates the amount of corneal astigmatism induced by pterygium increases with the increase in length of pterygium. The mean postoperative astigmatism at 3rd month in Groups A, B, and C were 0.479 ± 0.078 D ($P < 0.05$), 0.918 ± 0.128 D ($P < 0.0001$), and 3.41 ± 1.060 D ($P < 0.001$), respectively. Thus, a significant reduction in corneal astigmatism was seen 3 months after surgery more significantly in Groups B and C [Table 2]. It was observed that the mean preoperative refractive cylinder of 2.76 ± 0.33D as measured by autorefractometry reduced to 1.093 ± 0.12 D ($P < 0.0001$) postoperatively, which was statistically significant as in Table 3. TIA and DV between preoperative and 3 months postoperatively refractive astigmatism was calculated using Alpins single – Angle plots with AstigMATIC software (AstigMATIC is programmed in MATLAB R2018a (Mathworks Inc., Natick, MA, USA)) [Figure 1].

A statistically significant positive correlation was seen between the length of the pterygium and both preoperative ($\rho = 0.680, P < 0.0001$) and postoperative ($\rho = 0.53, P < 0.0001$) corneal astigmatism [Table 4].

DISCUSSION

Pterygium is a degenerative condition of the subconjunctival tissues which proliferates as vascularized granulation tissue to invade the cornea, destroying the superficial layers of the stroma and Bowman's membrane. It is more common in dry sunny climates, ultraviolet light being an etiological factor. The working hypothesis is that Ultraviolet (UV) radiation causes mutations in the p53 tumor suppressor gene, thus facilitating the abnormal proliferation of limbal epithelium.[7,13] As the disease progresses, the lesion increases in size and becomes more apparent to the naked eye and cosmetically unpleasant for the patient. Further growth may cause diminished vision due to induced astigmatism or direct encroachment onto the visual axis.

In our study, pterygia were more common in the age group of 46–65 years (27%). Females (75%) outnumbered males (25%) probably because they seek surgical intervention for cosmetic reasons. More cases were reported among the farmers and laborers which are in accordance with other studies and shows association with ultraviolet light exposure, low humidity, and dust.[5]

Avisar *et al*. observed 94 eyes with unilateral primary pterygium of different sizes. They found significant astigmatism in 16.6% with pterygium of 0.2–1 mm size, 45.45% in 1.1–3 mm size, and 100% in 5.1–6.7 mm in size. They suggested early surgical intervention in lesions >1 mm size from the limbus.[14] In our study, all eyes had nasal primary pterygia with a mean size of 2.7 ± 0.12 mm, of which Group A (<2 mm) had 12 eyes (13%), Group B (2–4 mm) had 52 eyes (71%), and Group C (>4 mm) had 11 eyes (16%), respectively.

Pterygia cause corneal distortion which results in with-the-rule astigmatism more often due to flattening of horizontal meridian.[15] However, against-the-rule and oblique astigmatism have also been recorded in patients with pterygia.[16] In our study, preoperatively 48 cases (64%) had with-the-rule astigmatism which confirms the finding as in previous studies.

The mean preoperative UCVA of 0.52 ± 0.06D and 0.33 ± 0.14D in Groups B and C significantly improved at 3rd month postoperatively by 0.798 ± 0.06D and 0.57 ± 0.18D ($P < 0.0001$). The UCVA remained the same in Group A with $\rho = 0.023$ which indicates less correlation between astigmatism induced by Grade I pterygia and UCVA. It is also observed that as the length of the pterygium increases, the mean UCVA decreases. These observations were comparable with the studies carried out by Maheshwari and Dr. Anwar hussain *et al*.[2,15]

A study by Lin and Stern showed a significant correlation between the pterygium length and corneal astigmatism, they reported significant degrees of induced corneal astigmatism seen in pterygium once it exceeded >45% of the radius of cornea or within 3.2 mm of the visual axis.[16] As Keratometry measures, only the central cornea and peripheral cornea is ignored, more erroneous results are seen in eyes with pterygium. Hence, computerized videokeratography remains the best tool for evaluating corneal astigmatism which was a limitation in our study.[17]

Hanson and Norn reported that pterygium >3.0 mm induced 1.97D of astigmatism versus 1.11D in <3 mm.[18] Kampitak reported a 2 D or more of astigmatism with length >2.25 mm.[9] Recently, Jaffar *et al.* found a strong correlation with a mean length of 2.84 ± 0.557 mm and inducing a 3.46 ± 1.441 D ($P = 0.01$) of astigmatism.[19] Similar observation was made in this study, where Groups B and C had preoperative astigmatism of 2.197 ± 0.71 D, and 5.9 ± 3.305 D, respectively compared to Group A which had 1 ± 0.469 D of corneal astigmatism. This proves that pterygia of length <2 mm induces less astigmatism compared to those of 2 mm–>4 mm.

Pterygium surgery significantly reduces corneal astigmatism.[20] There was a significant reduction of corneal astigmatism 3 months postoperatively after pterygium excision with conjunctival autograft. The difference between pre and postoperative astigmatism was 0.4791 ± 0.1582D in Group A, while it was 1.283 ± 0.2504D–2.5 ± 0.579D in Groups B and C respectively, the difference being statistically significant ($P < 0.0001$).

Mohammad-Salih and Sharif reported that the pterygium length has a stronger correlation with corneal astigmatism than does width.[21] Han *et al*. multivariate analysis revealed that only the length of pterygium was a significant predictive factor of pterygium-induced astigmatism.[22] In our study, a positive correlation between the pterygium length and preoperative ($\rho = 0.68$, $P < 0.0001$) and postoperative ($\rho = 0.53$, $P < 0.0001$) corneal astigmatism 3 months after surgery was observed. Patients requiring cataract surgery with Grade I, atrophic and nonprogressive pterygium can undergo cataract surgery directly.[2] However, Grade II pterygium or larger significantly affects the refractive component of the cornea leading to erroneous intraocular lens power calculation and postcataract refractive surprise. Hence, it is preferable to undergo pterygium excision before undertaking cataract surgery in such patients. By time-course analysis, cornea has been shown to stabilize 1 month after pterygium surgery.

CONCLUSIONS

Primary pterygium of more than 2.0 mm in length from the limbus, induces with-the-rule astigmatism (>2.55 ± 0.364 diopters). This significant astigmatism increases with the increase in length of the pterygium. A positive correlation between the pterygium length and preoperative ($\rho = 0.68$, $P < 0.0001$) and postoperative ($\rho = 0.53$, $P < 0.0001$) corneal astigmatism 3 months after surgery was observed. Keratometric astigmatism shows improvement or reduction 3 months after pterygium excision by conjunctival autograft technique with autologous blood. The findings in this study suggest an early surgical pterygium removal is indicated for pterygia of length >2 mm from the limbus.

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Conflicts of interest

There are no conflicts of interest.

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Phacocapsulectomy: A novel technique to deal with extensive capsular fibrosis

ABSTRACT

To describe a new technique of performing capsulotomy with phacoemulsification probe in cataracts with extensive capsular fibrosis. After making two side ports and a 2.2-mm temporal limbal incision, the phaco probe is inserted into the eye. An initial cut is made on the fibrosed anterior capsule with the phacotip. Subsequent cuts are made in the same plane to create a central opening which is of 5–5.5 mm size. This opening is quite stable as it is surrounded by fibrous tissue. Phacoemulsification and intra-ocular lens implantation can be safely done through this opening without damaging the integrity of the capsular opening. We have performed phacocapsulectomy in four such cases. All of them gained best-corrected visual acquity better than 20/40 at 3 months of follow-up. Creating a capsular opening in a cataract with extensive anterior capsular fibrosis is always challenging. Phacocapsulectomy can be a very useful method in dealing such cases.

Keywords: Anterior capsular fibrosis, phacocapsulectomy, phacoemulsification

INTRODUCTION

Fibrosis is a pathological condition characterized by excessive production and accumulation of collagen, loss of tissue architecture, and organ failure in response to uncontrolled wound healing.[1] Fibrosis on the anterior capsule of the human crystalline lens though rare in occurrence, but can be found in traumatic, hypermature, and long-standing cataracts. Capsulorhexis in the presence of anterior capsular fibrosis is always challenging. Any pull on the fibrosed area by capsulotomy needle or forceps may result in stress on the zonules as well as increased the propensity of the rhexis margin to run into the periphery. In these situations, the most commonly applied tool is a micro-scissors which cuts the fibrosed portion and helps in completion of the capsular opening with the help of forceps. Radio-frequency diathermy and Fugo blade are also capable of producing capsulorhexis in these challenging situations.[2,3] We are describing a technique where phacoemulsification probe has been used effectively to produce decent capsular opening in cases of extensive anterior capsular fibrosis.

SURGICAL TECHNIQUE

We hereby describe a case series of four patients where extensive anterior capsular fibrosis was noted and we applied our technique "phacocapsulectomy" to perform the anterior capsulotomy. A single experienced surgeon (NB) performed all the cases under peribulbar anesthesia. After making the two-side port incision, the trypan blue dye was injected to stain the anterior capsule [Video File 1]. A temporal limbal 2.2 mm main incision was created with

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a dual bevel keratome. The phacoemulsification probe (Centurion Vision System, Alcon laboratories, USA) with parameters set as: Power 70% OZIL, vacuum 80 mm Hg, flow rate 30 and IOP 50 mm Hg, with bevel up was introduced inside the eye. With continuous irrigation on, we press the food pedal to third position to puncture the anterior capsule [Figure 1a]. The initial puncture gives an idea of the thickness of the anterior capsule, and subsequent cuts are made exactly on the thickened, fibrosed capsule in a very controlled manner [Figure 1b]. Special care was taken to involve just the anterior capsule only, not the nucleus. Short burst of phaco energy was delivered in bevel up position, with moderate vacuum, taking care not to pool the nucleus with the phaco probe [Figure 1c and d]. A 5–5.5 mm capsulorhexis was created by taking subsequent cuts exactly on the anterior capsule with the phaco probe [Figure 1e and f]. Though the opening is not as smooth and stretchable as in conventional capsulorhexis, but the margins are quite strong and they did not give away during the subsequent steps. After finishing the capsulotomy, without doing any hydro procedure we started the nucleus management. First, we chopped the nucleus into different small pieces using chop *in situ* technique [Figure 2a and b],[4] and the pieces were emulsified subsequently with the parameters of power: OZIL 70%, vacuum 400 mmHg, aspiration flow rate 20, IOP 50 mmHg [Figure 2c and d]. A foldable hydrophobic intra-ocular lens (IOL) was implanted into the capsular bag [Figure 2e and f] using hydroimplantation technique.[5] Although the areas around the capsular opening are quite opaque, no attempt is made to remove those opaque areas. Preservative free 0.1 ml moxifloxacin (Vigamox, Alcon laboratories, Inc.) was injected into the anterior chamber to prevent the postoperative endophthalmitis. The main and side port incisions were sealed with stromal hydration. Postoperatively, the patients were prescribed 1% prednisolone acetate (Predforte, Allergan India,) eye drops for 6 weeks in a tapering dose and 0.5% moxifloxacin (Vigamox, Alcon laboratories, Inc.) eye drops 4 times/day for 4 weeks.

We have been able to complete the capsulorhexis in all four cases without any complications and the phacoemulsification with IOL implantation was also uneventful. At 3-month postoperative follow-up, all patients gained best-corrected visual acquity of more than 20/40 without any significant postoperative complications [Table 1].

DISCUSSION

Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process. Fibrosis of the anterior capsule in traumatic cataract is a typical example of reparative type of fibrosis.[1] This fibrosis may involve a part or the entire area of anterior capsule and the area under fibrosis may become thick and wrinkled. In sclerotic type of hyper mature cataract, the cortex becomes disintegrated and the lens becomes shrunken due to leakage of water, the anterior capsule becomes thickened and fibrosed.[6] Creating a capsulorhexis in these kinds of fibrosed capsule is a challenging job even for an experienced surgeon. If the fibrosis is at the center and occupies <5 mm of circumference, capsulorhexis can be performed by avoiding the fibrosed area. The situation is not so favorable in those cases where the fibrosis involves the whole or some parts of the capsulorhexis track. Forceps, scissors, and micro-rhexis forceps are useful tools in cutting and creating central opening in the presence of extensive anterior capsular fibrosis. However, this needs very controlled exercise, and in many a times, the capsular opening may not be a

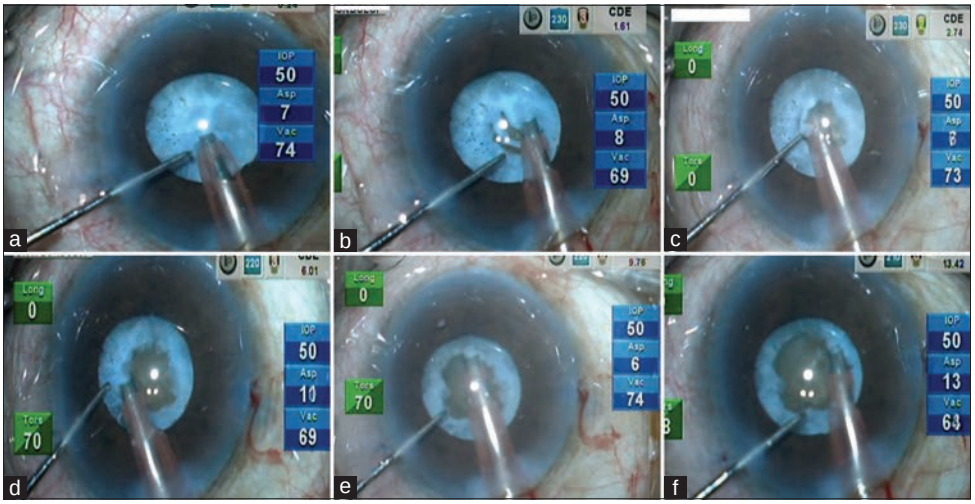


Figure 1: (a an b) Anterior capsule punctured with the phaco probe in bevel up position, (c and d) Subsequent cuts are make exactly on the anterior capsule taking care not to involve the nucleus, (e and f) Enlarging the capsular opening solely by the phaco probe

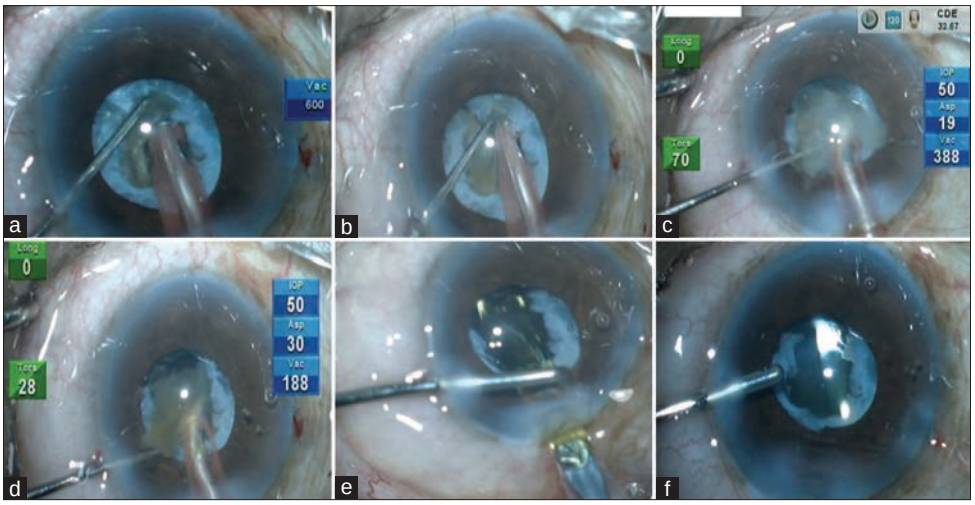


Figure 2: (a and b) The nucleus is chopped into different small pieces using chop *in situ* technique, (c and d) the nuclear fragments are being emulsified, (e and f) A foldable, hydrophobic, acrylic intraocular lens implanted in the capsular bag

Table 1: Summary of all cases

Age/ sex (years)	Cataract grade	Capsular fibrosis	Preoperative BCVA	Preoperative ECD	Phacocap	BCVA postoperative 3 months	ECD postoperative 3 months
69/female	HMC	Extensive	PL+	2300	Yes	20/40	2145
71/male	HMC	Extensive	PL+	2345	Yes	20/32	2198
76/male	HMC	Extensive	HM	2176	Yes	20/125	2012
82/female	HMC	Extensive	PL+	2098	Yes	20/32	1990

HMC - Hypermature cataract; BCVA - Best-corrected visual acquity; ECD - Endothelial cell density; Phacocap - Phacocapsulectomy; HM - Hand motions; PL - Perception of light

sufficient enough to complete the surgery. Radiofrequency capsulotomy and Fugo blade have been tried to overcome this issue with variable success.[2,3]

In this report, we are describing a new technique where a phacoprobe has been used to create a capsulorhexis in cases of extensive fibrosis involving the 360 degree of the anterior capsule. There are published reports, where phacoemulsification probe has been used to perform a capsulorhexis in intumescent white cataract.[7,8] In this technique, puncturing the anterior capsule and subsequent aspiration of the cortical material with the phaco probe brings down the intra-lenticular pressure, followed by completion of capsulorhexis with a rhexis forceps. This does not apply in our cases where the major challenge is the thick anterior capsule, not the high intra-lenticular pressure. The main modification in our technique that we have completed the full 360° rhexis with phaco probe only, we did not use any forceps or needle. In every case, initially we tried to puncture the capsule with the cystotome, but as soon as we feel the resistance, we immediately shift to phaco probe to perform the capsulorhexis. By targeting the anterior capsule with short burst of phaco energy, we have minimized the zonular stress. However, the theoretical risk of zonular dehiscence will be present, if excessive energy with high vacuum is given during phaco capsulectomy.

To best our knowledge, this is the first time, a phacoemulsification probe has been used to create a capsular opening in cataracts having extensive anterior capsular fibrosis. This is a safe, easy, controlled does not require any other instruments to produce these central openings.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Trochlear nerve palsy with contralateral Horner's syndrome: A rare presentation post trauma

ABSTRACT

We describe a case of posttraumatic vertical diplopia and Horner's syndrome (HS). The patient presented 2 weeks post road traffic accident with acute onset double vision more in left gaze and right tilt. The left eye had mild ptosis. The apparent elevation deficit in the left eye in levoelevation was misinterpreted as left eye superior rectus paresis instead of right eye inferior oblique overaction and thus mimicked superior division third nerve palsy in the left eye. Anisocoria was more in the dark. Computerized tomography of the brain and orbit was normal. Magnetic resonance imaging of the cervical spine showed left C6–C7 nerve root avulsion. A diagnosis of right fourth nerve palsy with left eye HS secondary to brachial plexus injury was made. We could not find a previous description of fourth nerve palsy with contralateral HS following trauma in the literature.

Keywords: Brachial plexus injury, Horner's syndrome, trochlear nerve palsy

INTRODUCTION

Trochlear nerve palsy may be congenital or acquired. The causes of acquired trochlear nerve palsy are vascular injury, trauma specifically closed head trauma, intracranial space-occupying lesions, demyelination etc., Trochlear nerve palsy is the most common cause for a single cyclovertical muscle palsy. Posttraumatic isolated trochlear nerve palsies are usually seen in closed head injuries.[1] Approximately 18% of all trochlear nerve palsies are due to trauma.[2] We describe a case of posttraumatic ptosis with vertical diplopia that caused a confusion in the diagnosis. The patient presented with left head tilt with right hypertropia more in left gaze and right tilt. The patient had mild ptosis with miosis in the left eye that was secondary to Horner's syndrome (HS) associated with brachial plexus injury. HS is common in injuries to the brachial plexus.[3,4] Acquired trochlear nerve palsy with ipsilateral HS was previously reported in brainstem stroke and cavernous sinus lesions.[5-7] Trochlear nerve palsy with contralateral HS has also been described in the literature.[8,9] However, we were unable to find any reports of trochlear nerve palsy with contralateral HS following trauma in the scientific literature.

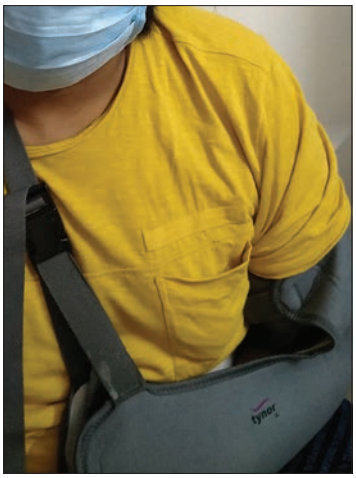


Figure 1: Left brachial plexus injury

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CASE REPORT

A 21-year-old male with a history of fall from a motorcycle 2 weeks back was referred to our outpatient department with complaints of binocular vertical diplopia. There was no history of loss of consciousness, vertigo, or vomiting. He had paresis of left upper limb secondary to left brachial plexus injury [Figure 1] with left C6 and C7 nerve root avulsion. The best-corrected visual acuity was 6/6 in both eyes. The anterior segment was normal except for anisocoria with the left pupil smaller than the right. The direct and consensual pupillary reactions and posterior segment were normal.



Figure 2: Left head tilt

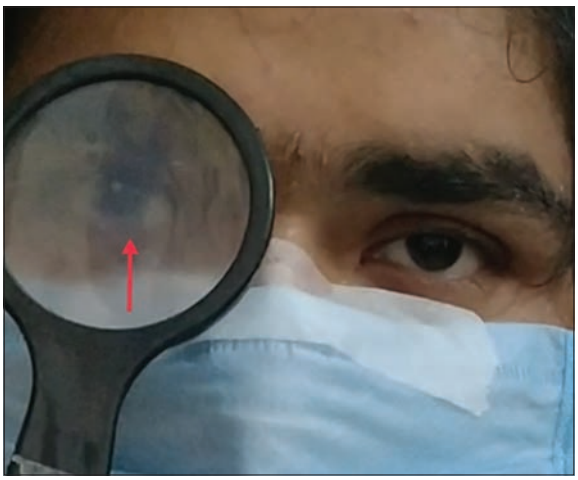


Figure 3: Right hypertropia

The patient had a left head tilt with mild ptosis in the left eye [Figure 2]. The Hirschberg reflex was central, and the cover test revealed right hypertropia [Figure 3]. The right side appeared more hypertropic on general examination because the inferior limbus to lower lid margin was higher on the right side. The Parks three-step test showed right hypertropia more in left gaze and right tilt [Figures 4 and 5], suggestive of right trochlear nerve palsy. Figure 6 shows the nine cardinal gazes. Extraocular movements were full except for apparent elevation deficit in the left eye which was due to the inferior oblique overaction in the right eye secondary to right superior oblique underaction. The computerized tomography image of the brain and orbit was normal [Figure 7]. The forced duction test under topical anesthesia did not show any restriction.

Diplopia charting [Figure 8] showed crossed diplopia with right hypertropia more in left gazes, maximum being in the levoelevation, suggesting right inferior oblique overaction secondary to SO palsy. The apparent elevation deficit in the left eye with ptosis was initially provisionally diagnosed as superior division third nerve paresis of the left eye.

A detailed orthopedic evaluation was done. Magnetic resonance imaging of the cervical spine showed left C6–C7 nerve root avulsion with pseudomeningocele [Figure 9].

The left eye also showed inverse ptosis with the lower lid margin to the inferior limbus distance being less on the left side. The anisocoria [Figure 10] was more in dark compared to bright light. The findings of mild ptosis and miosis in the left eye with adduction being normal led to the diagnosis of HS secondary to the left brachial plexus injury and excluded a diagnosis of superior division third nerve paresis.

A final diagnosis of post traumatic fourth nerve palsy in the right eye associated with left eye HS secondary to brachial plexus injury was made.



Figure 4: Right hypertropia more in left gaze

DISCUSSION

Isolated fourth nerve palsy either unilateral or bilateral can occur following head trauma.[1,10] It usually presents with vertical diplopia with hypertropia more in the opposite gaze and same side tilt (Parks-Bielschowsky test) and excyclotorsion. Bilateral palsy is common in closed head injuries as the two nerves decussate at the anterior medullary velum.[11] Patients usually present with V pattern esotropia with torsional diplopia and >15° extorsion. Hypertropia usually prominent in one eye reverses in side gazes. We should always suspect bilateral injury if the hypertropia reverses in any of the nine cardinal gazes.[12]

Usually superior oblique palsy causes double vision more in downgaze. It is unusual to have an inferior oblique overaction secondary to a traumatic superior oblique palsy within few days of trauma. In this case, the inferior oblique overaction was more which resulted the maximum separation of images in the levoelevation and misinterpreted as left eye superior rectus underaction in the diplopia chart. Superior rectus involvement with ptosis led to a diagnostic dilemma.



Figure 5: Right hypertropia more in right tilt

About 12% of all third nerve injuries are due to direct injuries such as trauma, indirect injuries such as compression, and ischemia at different sites. Isolated traumatic third nerve palsies are usually associated with intracranial injuries or even minor head trauma and orbital injuries.[13,14] Isolated oculomotor palsies are mostly basilar. Complete third nerve palsy presents with complete ptosis with or without mydriasis and the eye adopting a down and out position due to the uninvolved lateral rectus and superior oblique function. Partial third nerve palsies present with similar features but to a lesser extent.

Patients usually adopt a head posture in paralytic strabismus either to improve their binocular field or to separate the images extremely far to avoid double vision. The head tilt in this case was due to superior oblique palsy.



Figure 6: Extraocular movements in nine cardinal gazes - RE SO underaction with IO overaction, LE - apparent SR underaction



Figure 7: Normal computed tomography brain and orbit

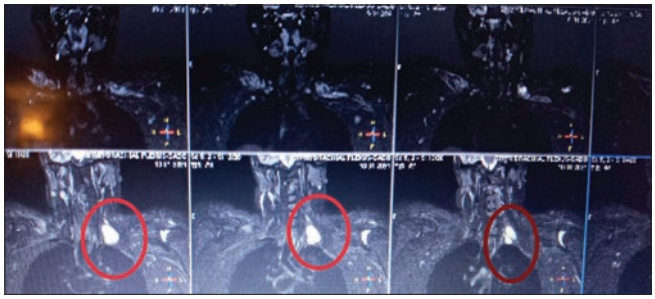


Figure 9: Magnetic resonance imaging cervical spine-C6, C7 nerve root avulsion with pseudomeningocele

HS, a triad of ptosis, miosis, and anhidrosis, results from the interruption of the sympathetic chain from eye to the hypothalamus.[15] Ptosis is usually mild (<2 mm) as the tone sympathetically innervated Muller's muscle causing the initial elevation of the eye is lost. In this case, the lower lid to the inferior limbus distance was more in the right eye, confirming an upside down or inverse ptosis [Figure 11] in the left eye. The pupil in HS will be small on the involved side due to the loss of sympathetic tone of the dilator pupillae, but direct and consensual reactions will be normal. The anisocoria will be more in dark, as the parasympathetic tone will be more in dark. Lesions anywhere in the oculosympathetic pathway results in central (first order), preganglionic (second order), or postganglionic (third order) HS. The present case had an injury to the brachial plexus and is a second-order HS.

Fourth nerve palsy with ipsilateral Horners has been previously described in a case of brain stem strokes and cavernous sinus involvement such as tumors and Tolosa-Hunt syndrome.[5-7]

Trochlear palsy with contralateral HS has been described by Guy *et al*. in two patients, one with arteriovenous malformation and the other with a mass in the brain stem.[8]

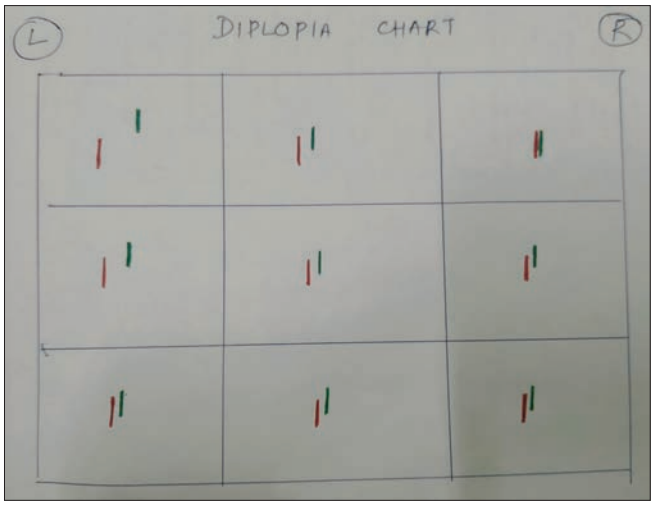


Figure 8: Diplopia chart showing maximum separation of images in the levoelevation

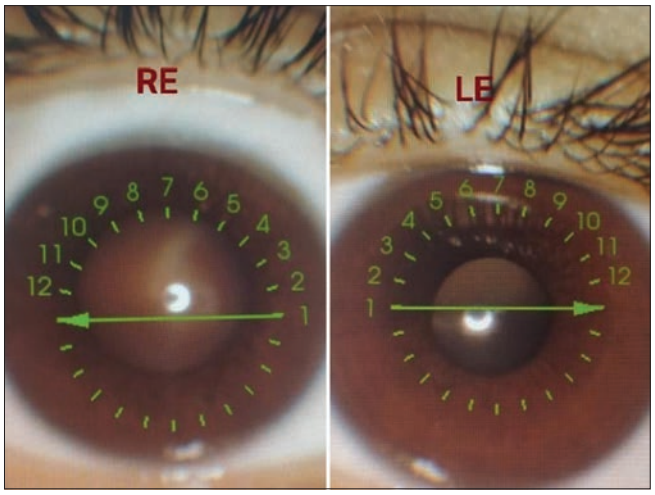


Figure 10: Anisocoria with left eye miosis

Recently, a similar case has been described with mesencephalic hemorrhage as the etiology.[9] In all these cases, the presentation has a localizing value. However, in this case, both are two separate entities presenting in the same patient. Neurological imaging is necessary to find the causes of combined fourth nerve palsy and HS.

CONCLUSION

Proper assessment of ocular motility and assessment of associated ocular and systemic findings are necessary to arrive at the correct diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name



Figure 11: Inverse ptosis left eye

and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Capillary hemangioma masquerading as a dermoid cyst

ABSTRACT

Capillary hemangioma occurs in 1%–2% of neonates and in 10%–12% of infants within 1st year of life. They may present as a cutaneous, subcutaneous, or orbital lesion. The most common sites are eyelid or brow, with a predilection for the upper eyelid. We hereby report a case of a 1-year-old female child presenting in our outpatient department with swelling over the left eyebrow since birth gradually increasing in size. The lesion was firm in consistency, slightly mobile, nontender, superior orbital margin nonpalpable. Based on imaging, a diagnosis of dermoid cyst was made, but on excision, there was an absence of capsule surrounding it with positivity for human glucose transport protein 1 (GLUT1) on histopathology changing the diagnosis to hemangioma.

Keywords: Dermoid cyst, hemangioma, masquarade

INTRODUCTION

Capillary hemangioma is one of the most common benign periocular and orbital (CH) vascular tumors of childhood. In most of the cases, the natural progression starts with enlargement followed by spontaneous lapse without management over a period, without sequelae. Cutaneous Capillary hemangioma (CHs) can present as a small, red, raised isolated lesion, or as dark blue subcutaneous lesions and may extend into the orbit or huge mass that can result in visual impairment or rarely might be associated with systemic impairment or syndrome. We, hereby, describe the case report of a capillary hemangioma masquerading as a dermoid cyst.

CASE REPORT

A 1-year-old female child presented in our outpatient department with swelling over the left eyebrow since birth gradually increasing in size. The vision and ocular examination of both the eyes was unremarkable except that there was a circumscribed lesion over the left eyebrow superomedially of approximately 2.5 cm in diameter, nonerythematous, smooth counter, with normal overlying skin and no dilated blood vessels over the surface. The lesion was firm in consistency, slightly mobile, nontender, superior orbital margin nonpalpable [Figure 1a]. The systemic examination was within normal limits. On doing noncontrast computed tomography (CT), orbit large ovoid soft-tissue, low-attenuation lesion in the medial aspect of the left orbit, measuring 2.1 cm × 2.9 cm, with no lobules/septa was seen with a differential diagnosis of angular dermoid [Figure 1b]. Excision biopsy of the mass was planned. Intraoperatively, an ill-defined mass with lobular appearance was noted, it was firmly attached to the underlying muscle. There was no surrounding capsule that doubted the presence of a dermoid cyst. A punch biopsy was taken and sent for histopathological examination [Figure 1c]. Histopathological examination revealed in (i) lobules of dilated capillaries extending into adjacent skeletal muscle bundles and adipose tissue. These capillaries are lined by plump endothelial cells. (ii) The cells are positive for GLUT 1, which is suggestive of hemangioma.

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Figure 1: (a) Preoperative photograph of the child revealing well-circumscribed lesion over the left eyebrow superomedially of size approximately 2.5 cm in diameter, nonerythematous, smooth contour. (b) Noncontrast computed tomography orbit showing large ovoid soft-tissue, low-attenuation lesion in the medial aspect of the left orbit, measuring 2.1 cm × 2.9 cm, with absence of lobules/septa seen. (c) Histopathological examination shows in (i) lobules of dilated capillaries extending into adjacent skeletal muscle bundles and adipose tissue. These capillaries are lined by plump endothelial cells. (ii) The cells are positive for GLUT 1 suggestive of hemangioma. (d) Postoperative photograph of the child showing regression of size of the cyst

The child was started on oral propranolol (in supervision of pediatrician for appropriate dosage) and topical timolol 0.25% after clearance from a cardiologist. The child is on regular follow-up with us and the size of lesion has decreased [Figure 1d].

DISCUSSION

Capillary hemangioma occurs in 1%–2% of neonates and in 10%–12% of infants within the 1st year of life. They may present as a cutaneous, subcutaneous, or orbital lesion.[1] Most common sites are eyelid or brow, with a predilection for the upper eyelid. Most often, natural course involves proliferative phase for initial 1 year, followed by stabilization and spontaneous involution over several years. Dermoid cysts are the congenital choristomas of orbit. Nearly 7% of the dermoid cyst occur in the head-and-neck region and 70% of the dermoids that occur in the periorbital region have a common location preference for the extra angular region.[2] They generally arise at birth but may not be apparent until the first decade of life due to their location in deeper plains.[3] A careful clinical examination including proper history for age of onset, color, and location is mandatory. If inconclusive, diagnostic modalities such as CT scan and magnetic resonance imaging should be undertaken. In the current case, the consistency of the cyst and CT scan misguided the ophthalmologist,[4] the absence of capsule while taking excision biopsy and its firm attachment to muscle with absence of teratogenic tissue in the form of hairs made the surgeon suspicious for presence of infantile hemangioma that was confirmed by histopathological examination. This similar finding of a dermoid cyst being misdiagnosed as capillary hemangioma has also been reported by Hsu and Mohney and Al-Muhaylib *et al*. in a 3-month and a 3-year-old female child, respectively.[2,5]

Hence, an appropriate clinical imaging is important to make an accurate diagnosis, and infantile hemangioma should be kept as an important differential diagnosis in case of periocular swellings as the management of both the entities completely varies.

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

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Case Report

The damaging shield: An incapacitating presentation of vernal keratoconjunctivitis

ABSTRACT

Vernal keratoconjunctivitis (VKC) is a recurrent, bilateral, seasonal disorder which mostly affects young males. Shield ulcer is an uncommon manifestation of severe form of VKC, seen in 3%–11% of VKC patients, which adversely affects vision. The purpose of this case report is to bring to light that proper timely management can improve visual acuity. A 15-year-old male presented with a complaint of severe itching, with foreign body sensation and redness in BE since 1 week. It was associated with blurring of vision in LE since 2 days. He had history of similar episodes since the past 7 years, usually exacerbating in spring for which he was advised topical steroids and lubricating drops. On examination, RE showed papillae in both upper and lower tarsal conjunctiva. LE showed lid edema, giant cobblestone appearance of papillae in upper and lower tarsal conjunctiva, and a fluorescein stained positive epithelial defect of 3 mm × 4 mm which had elevated plaque containing mucus and debris was noted in the central cornea. He was diagnosed with bilateral VKC with Grade 3 shield ulcer in LE. He was started on topical steroid 4 times and lubricating drops in BE along with topical tacrolimus 0.03% BD in LE. No improvement was noted after 3 days. Margin and base of ulcer with 1 mm of clear margin was scraped and bandage contact lens was put on the 3rd day of starting treatment. On 1 week follow-up of scraping, healing margin was noted with best-corrected visual acuity (BCVA) of 6/60. After 1 month, the BCVA improved to 6/18, and at 3-month follow–up, it improved to 6/9. Shield ulcer, although rare, is an incapacitating vision threatening manifestation of VKC. Timely management of the same is essential to ensure full recovery without any permanent ocular damage. Conservative management should always be considered before surgical treatment in all cases. Various studies are being carried to study the efficacy of immunosuppressive agents especially tacrolimus in treating shield ulcer. Here, we found out that timely instillation of tacrolimus can lead to prompt recovery with significant visual rehabilitation.

Keywords: Giant cobblestone papillae, shield ulcer, vernal keratoconjunctivitis

INTRODUCTION

Vernal keratoconjunctivitis (VKC) was first described by Arlt in 1846. VKC is a chronic, recurrent, bilateral conjunctival inflammatory condition which usually affects population with atopy. It is also a seasonal disorder, mostly seen in Mediterranean area, West Africa and Indian subcontinent due to the hot and dry climate. About 45%–75% of patients with VKC have a history of atopy such as asthma, rhinitis, and eczema.[1] It is more common in males in younger population. Onset of the disease is generally before the age of 10 and lasts for 2–10 years. It resolves in late puberty and rarely seen after the age of 20 years. Shield ulcer is an uncommon manifestation of severe form of VKC, seen in 3%–11% of VKC patients. It can be a vision threatening complication of VKC which is divided into three grades by Cameron in 1995 according to its clinical features, treatment, and outcome.[2]

CASE REPORT

A 15-year-old male presented to ophthalmology outpatient department with complaint of severe itching foreign body

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sensation and redness in both eyes since 1 week. It was associated with blurring of vision in left eye since 2 days. He had a history of similar episodes since the past 7 years, for which he was advised topical steroids and lubricating drops. His best-corrected visual acuity (BCVA) in RE was 6/6 and in LE was finger counting at 3 m. On ophthalmic examination, RE showed papillae in both upper and lower tarsal conjunctiva and keratinization in upper conjunctiva [Figures 1 and 2]. LE showed lid edema, giant cobblestone appearance of papillae in upper and lower tarsal conjunctiva. A fluorescein stained positive epithelial defect of 3 mm × 4 mm which had elevated plaque containing mucus and debris was noted in the central cornea in LE [Figure 3]. He was diagnosed with bilateral VKC with Grade 3 shield ulcer in LE. He was then started on topical prednisolone 1% 4 times and lubricating drops in BE along with topical tacrolimus ointment 0.03% BD. No significant improvement was noted after 3 days. He was advised amniotic membrane with debridement. As the patient was unwilling for surgery, conservative management with debridement was tried. Margin and base of ulcer with 1 mm of clear margin was debrided and bandage contact lens was put on the 3rd day of starting treatment [Figure 4]. On 1 week follow-up, healing margin with BCVA of 6/60 was noted [Figure 5]. One month follow-up showed BCVA improving to 6/18 [Figure 6] and at 3 month follow-up, BCVA improved to 6/9 [Figure 7].

DISCUSSION

VKC is a recurrent, bilateral, seasonal, and atopic disorder. It is an allergic inflammatory condition affecting the tarsus and/or bulbar conjunctiva. It usually presents with severe itching, photophobia, ropy thick mucoid discharge, and foreign body sensation due to giant papillae (cobblestone appearance). It also affects the cornea, showing various manifestations such as Horner-Trantas dots, superficial punctuate keratitis, shield ulcer, corneal plaque, bacterial or fungal keratitis, keratoconus, hydrops, pseudogerontoxon, and corneal opacification. Shield ulcer is a frank corneal epithelial defect caused due to coalesce of punctate



Figure 1: Upper tarsal papillae in the right eye

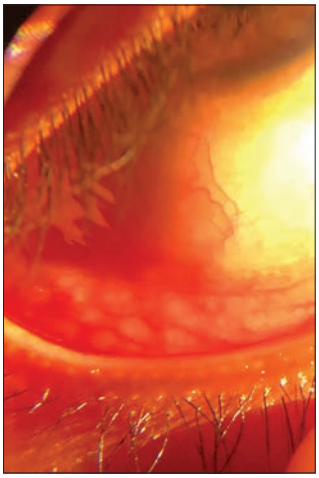


Figure 2: Lower tarsal papillae in the right eye

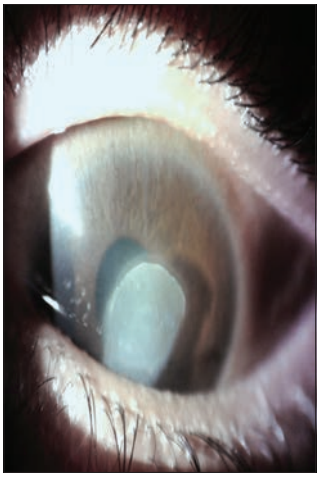


Figure 3: Shield ulcer in the left eye

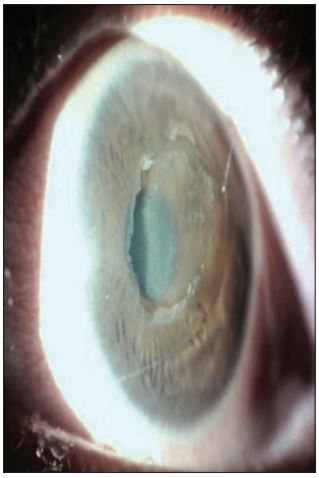


Figure 4: Left eye debridement of ulcer

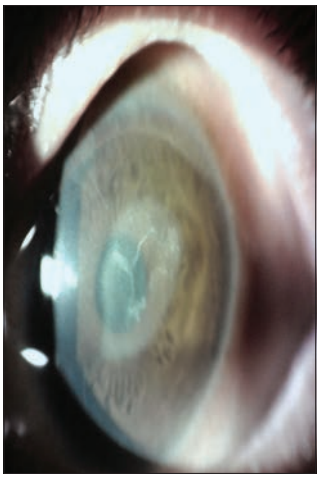


Figure 5: Left eye cornea on 1 week follow-up

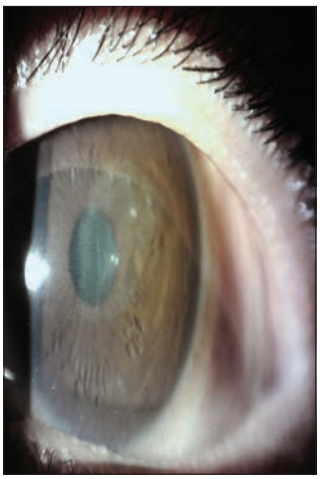


Figure 6: Left eye cornea on 1 month follow-up

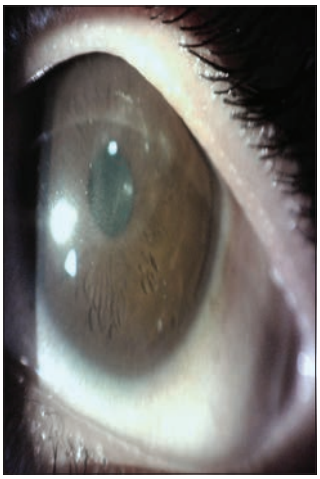


Figure 7: Left eye cornea on 3rd month of follow-up

epithelial keratitis. It is also known as Togby's ulcer. It does not affect the bowman's layer. It is known to be caused due to two different mechanisms, "mechanical" and "Toxin" hypothesis. Toxin hypothesis suggest that there is corneal epithelium damage due to inflammatory cells, cytokines, and chemokines liberated from T helper type 2 cells. Mechanical hypothesis suggest that giant papillae on the upper tarsal conjunctiva erode the corneal epithelium.[2] This also explains the superior corneal location of the ulcer. It usually has its lower border in half of the visual axis. If it is left untreated, a plaque formation occur containing fibrin and mucus over the epithelial defect causing delayed re-epithelization. Shield ulcers without plaque formation usually have a good visual outcome due to rapid re-epithelialization.[3]

Cameron has classified shield ulcer into three grades: Grade 1-Ulcer with transparent base. They undergo rapid re-epithelization with medical treatment alone. Mild scarring might occur but no other complications. They have good visual outcome.[2] Grade 2-Ulcer with translucent base or ulcer with opaque white or yellow deposits. They undergo delayed re-epithelization and need medical treatment with simple surgical management like scraping. Complications such as bacterial keratitis, amblyopia, strabismus, corneal vascularization, and residual corneal scarring is seen in few patients.[2] Grade 3-Ulcer with elevated plaques above the level of the surrounding epithelium. These ulcers need prolonged treatment and often have to be managed surgically like debridement with amniotic membrane.[2] Avoidance of the allergens is the most important but not feasible treatment. Patients with severe inflammation or shield ulcer are started on topical steroid (fluorometholone 0.1%–0.25% or loteprednol 0.5% or prednisolone acetate 1% or dexamethasone 0.1% ointment) 4–6 times a day, +/- topical antibiotic and cycloplegic agent, cool compresses.[4] Steroids need to be monitored and tapered consciously. Cromolyn sodium, a mast cell stabilizer is also shown to be effective in VKC.[5] Topical calcineurin inhibitors such as cyclosporine A and tacrolimus have also been used.[6] Cyclosporine was noted to cause burning sensation so tacrolimus ointment 0.03% was tried due to its immunomodulatory functions, mainly inhibitory action on the formation of cytokines and release of histamines.[7]

Shield ulcer is a vision threatening complication of VKC and thus needs prompt and vigorous treatment to save the vision. In this case, a Grade 3 ulcer was managed efficiently by simple debridement and topical treatment. Thus, we can say that a trial of conservative management with debridement and bandage contact lens can be undertaken in Grade 3 shield ulcer.

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

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There are no conflicts of interest.

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Case Report

Abnormal electrophysiology in a case of torpedo maculopathy

ABSTRACT

Torpedo maculopathy is an uncommon, often isolated retinal finding reported in literature. We report a case of torpedo maculopathy with nystagmus and abnormal electroretinogram findings with an abnormal mutation in a child. This case highlights the need for a detailed evaluation including electrophysiology and genetic testing in this retinal pathology.

Keywords: Electrophysiology, RP1L1 mutation, torpedo maculopathy

INTRODUCTION

Torpedo maculopathy is a rare, incidental retinal finding believed to a presumably congenital lesion involving the retinal pigment epithelium (RPE)[1] with primary choriocapillary loss.[2] Retinal laser ellipsometry analysis has revealed a kite-shaped region at the junction of superior arcuate, inferior arcuate, and papillomacular bundle to be the location of this finding, a region of embryologically sparse nerve fiber layers.[3] Other ocular comorbidity and genetic analysis of these patients however are scarcely detailed in the literature.[4,5] We report a case of torpedo maculopathy associated with electrophysiological changes and genetic mutation not hitherto reported in literature.

CASE REPORT

A 5-month-old male child presented to our clinic with complaints of abnormal eye movements in both eyes noticed since birth. He was born of a full-term normal delivery with birth weight of 3.2 kg in a consanguineous family. There was no positive antenatal history. He was immunized for age and was diagnosed to have global developmental delay. On examination, he was fixing and following light and was noted to have large amplitude pendular nystagmus. Retinoscopy did not reveal any gross refractive error.

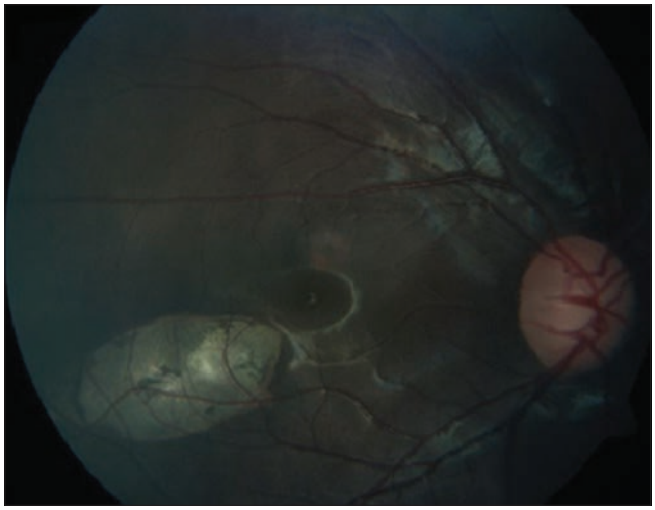


Figure 1: Fundus picture of the right eye showing torpedo-shaped hypopigmented atrophic patch with well-defined margins inferotemporal to fovea

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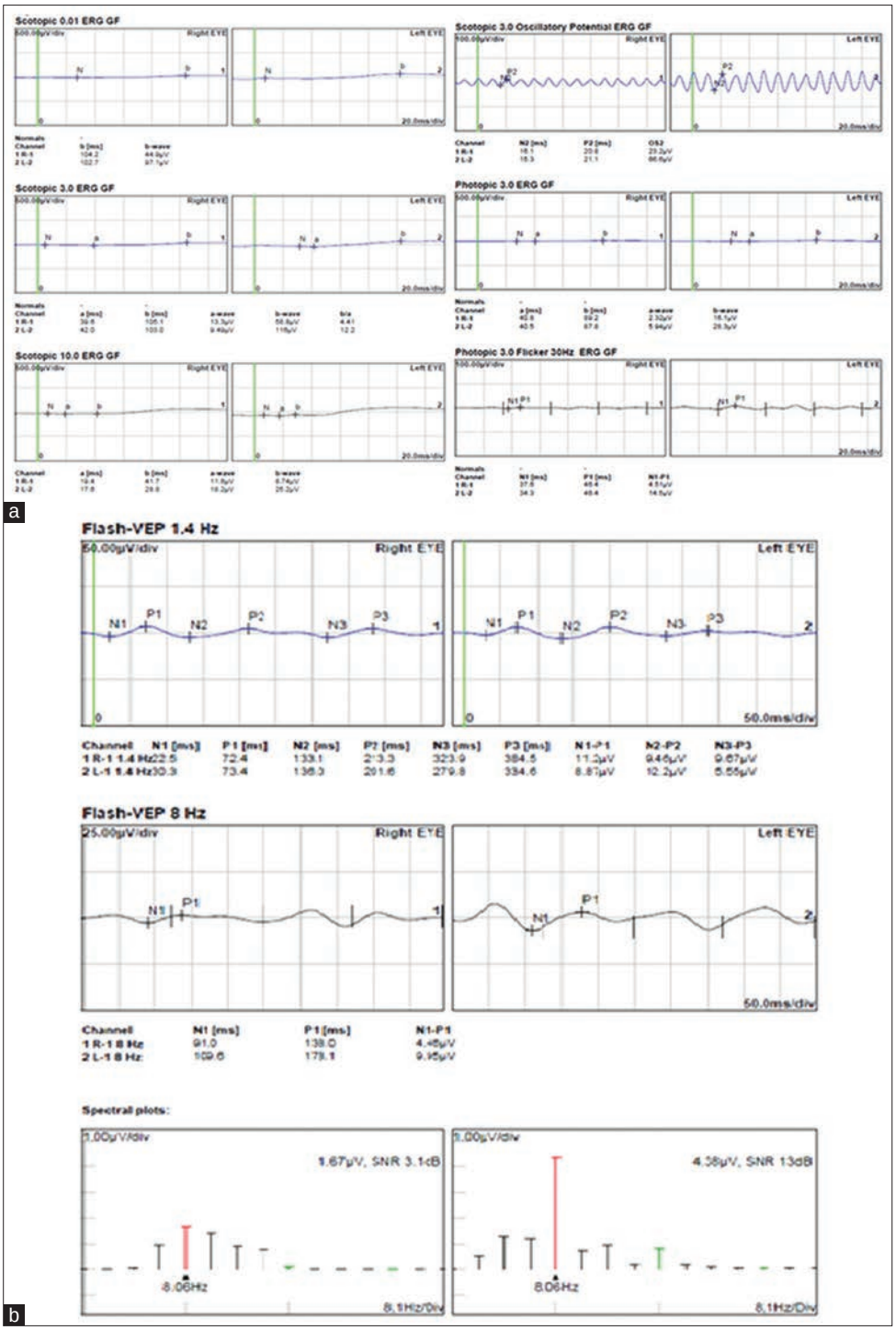


Figure 2: (a) Flash electroretinogram revealed suppression of both scotopic and photopic waveforms suggestive of rod-cone dysfunction; (b) Flash visual evoked potential showing abnormal irregular waveforms

Anterior segment examination was unremarkable with normal pupils in both eyes. Fundus examination revealed a large pale disc with myelinated nerve fibers inferior to the disc in both eyes. A torpedo-shaped hypopigmented atrophic patch with well-defined margins was noted inferotemporal to right eye fovea [Figure 1]. Flash visual evoked potential showed irregular waveforms and flash electroretinogram (ERG) revealed suppression of scotopic and photopic waveforms [Figure 2]. Optical coherence tomographic of the right eye [Figure 3] revealed type 1 pattern[6] with inner segment-outer segment irregularity, attenuation of the ellipsoid layer and interdigitation zone, RPE thinning and RPE choroidal excavation without any outer retinal cavitation. Pediatric neurology evaluation was done,

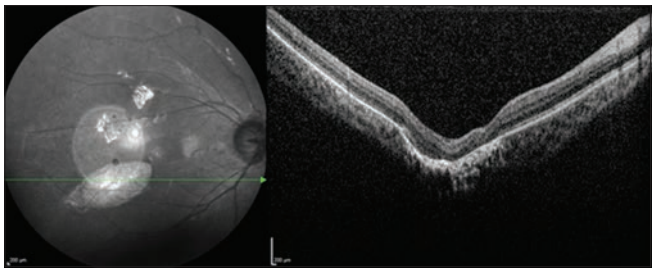


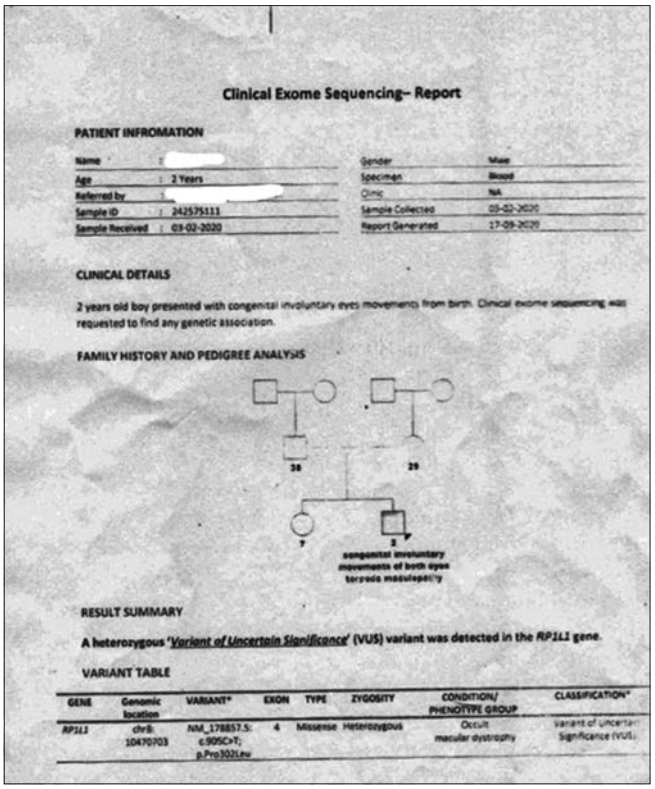
Figure 3: Optical coherence tomographic scan through torpedo maculopathy lesion showing normal inner retinal layers, outer segment abnormality with the loss of ellipsoid layer, interdigitation zone, retinal pigment epithelium thinning, and retinal pigment epithelium-choroidal excavation with no outer retinal cavitation (type 1 pattern)

and magnetic resonance imaging brain was normal. As a part of his systemic evaluation, chromosomal sequencing was done which revealed a heterozygous "variant of uncertain significance" variant in RP1sL1 gene [Figure 4]. Chromosomal evaluation of the parents and relatives could not be done. He was managed conservatively and followed up at 6 months interval.

DISCUSSION

We report a case of torpedo maculopathy with abnormal ERG findings associated with an RP1L1 mutation. Torpedo maculopathy is mostly an isolated retinal finding and is often reported as a stable pathology with recommended annual ocular follow-up. Reports of progression to retinal degeneration, retinal detachment, and choroidal neovascularization exist.[7,8] Cases of torpedo maculopathy with reported mutations have other systemic manifestations consistent with the mutations including autistic features, mental retardation, tuberous sclerosis, and retinal astrocytomas.[4,5] However, none of the reports have highlighted the role of electrophysiologic findings or associated ocular comorbidity.[7,8] Naik *et al*. had observed that one of their patients with enhanced s-cone syndrome had a torpedo lesion.[9] However, patients with RP1L1 mutations[10] have associated occult macular dystrophy and abnormal ERG even though clinically documented pigmentary retinopathy may be absent. The association of torpedo lesion with this mutation, however, has not been reported.

With this report and review of the previous relevant reports, we would like to emphasize that it may be necessary to do electrophysiological tests and genetic analysis in patients who are diagnosed to have torpedo maculopathy. Identification of the abnormal electrophysiology and/or genetic mutation could help us identify ocular or systemic pathologies that may be associated and may help us understand the related embryological events. The association of torpedo maculopathy with this mutation may


Clinical Exome Sequencing– Report

PATIENT INFROMATION

Name	: [redacted]	Gender	: Male
Age	: 2 Years	Specimen	: Blood
Referred by	: [redacted]	Clinic	: NA
Sample ID	: 242575111	Sample Collected	: 03-02-2020
Sample Received	: 03-02-2020	Report Generated	: 17-09-2020

CLINICAL DETAILS

2 years old boy presented with congenital involuntary eyes movements from birth. Clinical exome sequencing was requested to find any genetic association.

FAMILY HISTORY AND PEDIGREE ANALYSIS

RESULT SUMMARY

A heterozygous '*Variant of Uncertain Significance*' (VUS) variant was detected in the *RP1L1* gene.

VARIANT TABLE

GENE	Genomic location	VARIANT*	EXON	TYPE	ZYGOSITY	CONDITION/ PHENOTYPE GROUP	CLASSIFICATION*
RP1L1	chr8: 10470703	NM_178857.5: c.905C>T; p.Pro302Leu	4	Missense	Heterozygous	Occult macular dystrophy	Variant of uncertain significance (VUS)

Figure 4: Chromosomal sequencing revealing a heterozygous "variant of uncertain significance" variant in RP1L1 gene

be a chance occurrence in this case unless proved otherwise. A pooled genetic analysis of the reported cases of torpedo maculopathy may probably help us better understand the genetic predisposition of these rare eyes.

In summary, this case highlights two important observations. Patients with torpedo maculopathy must be tested electrophysiologically as there could be occult retinal dystrophies. These patients should also be appropriately investigated systemically as they may be associated with neurologic abnormalities and genetic mutations.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Nonpigmented immobile large vitreous cyst: A rare case report

ABSTRACT

Primary vitreous cysts are rare ocular manifestations. Often, they do not cause any visual disturbances. Vitreous cysts can be congenital or acquired. Here, we report the case of a 60-year-old male patient who presented to our outpatient department with a complaint of a bubble-like floater in his right eye which remained fixed despite movement of eyeballs. He had this visual disturbance for the past 20 years. The size and appearance of floater remained constant all these years. Aided visual acuity was 20/20 in both the eyes. Fundus examination showed the presence of a single transparent nonmobile cyst in the vitreous cavity of the right eye. Left eye fundus was normal. Right eye B-scan showed a nonmobile vitreous cyst abutting the optic nerve. The patient tested negative for *Echinococcus* and cysticercosis. As it was a primary vitreous cyst and the patient was asymptomatic, we decided to keep the patient under regular follow-up.

Keywords: Floater, immobile cyst, vitreous cyst

INTRODUCTION

Vitreous cysts are rare ocular manifestations. Patients having vitreous cysts are usually asymptomatic, but few patients can present with a bubble-like floater in front of the eyes. Visual acuity is not affected generally. Vitreous cysts are diagnosed on routine fundus examination. As they are mostly asymptomatic, management should be conservative. Invasive intervention is rarely required. Seldom, small fixed vitreous cysts have been reported in the past, although a large-sized fixed idiopathic vitreous cyst still remains a unique clinical finding. Here, we present a case of fixed, transparent vitreous cyst which generates curiosity given its large size.

CASE REPORT

A 60-year-old male patient presented to our outpatient department with a history of a bubble-like floater in his right eye for the past 20 years. There was no history of any systemic disorder, trauma, or infection in the eye. Vision was 6/6 in both the eyes. Intraocular pressure of the right and left eyes was 16 and 12 mmHg, respectively, measured with noncontact tonometer. The anterior segment of both the eyes was normal, with no signs of inflammation. Indirect ophthalmoscopy and posterior segment biomicroscopy were performed after dilation which showed a vitreous cyst in his right eye which was not changing its position with ocular movements. Fundus was normal in the left eye. No degeneration was detected in the peripheral retina of both the eyes. Fundus photograph showed a well-demarcated large vitreous cyst with a remarkable absence of any pigmentation. The surface wall of the cyst was smooth and transparent, with underlying retina clearly visible [Figure 1]. Right eye B-scan ultrasonography showed a well-defined cystic lesion measuring approximately 10.8 mm × 11.3 mm in the posterior chamber of the right eye [Figure 2]. The cyst was adherent to the posterior wall with no positional change on

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Figure 1: Large fixed vitreous cyst with underlying retina clearly visible

eyeball movement. There was no vascular uptake on colour doppler flow imaging (CDFI). Serology was negative for *Echinococcus* and cysticercosis. There was no eosinophilia on peripheral blood smear. Stool examination was negative for parasite ova. Based on these findings, the patient was diagnosed as idiopathic nonpigmented fixed vitreous cyst. As the patient had few symptoms, no active intervention was done. The patient is on routine follow-up.

DISCUSSION

Tansley was the first person to describe free-floating vitreous cyst in 1899.[1] Vitreous cysts can be classified into congenital or acquired. The congenital vitreous cysts further can be pigmented or nonpigmented. The former are believed to arise from the iris or ciliary body pigment epithelium.[2] On the contrary, the nonpigmented vitreous cysts are the remnants of the primary hyaloid vascular system such as Bergmeister's papilla and Mittendorf's dot.[3]

Acquired vitreous cysts are mostly associated with inflammatory conditions such as toxoplasmosis,[4] *Echinococcus,* and cysticercosis. They can also be associated with Intermediate uveitis,[5] degenerative diseases of the retina or choroid, retinal detachment surgeries, and ocular trauma. Trauma as a cause of vitreous cyst formation was first described by Awan in 1975.[6] Ocular trauma may cause the dislocation of already formed cyst.

An electron microscopic study of vitreous cyst by Orellana *et al*. hypothesized the origin of cyst to be pigment epithelium.[7]

Nork and Millecchia reported immature melanosomes in pigmented epithelium tissue on histopathological examination of vitreous cyst and put forth the hypothesis that it is choristoma of the primary hyaloid system.[8]

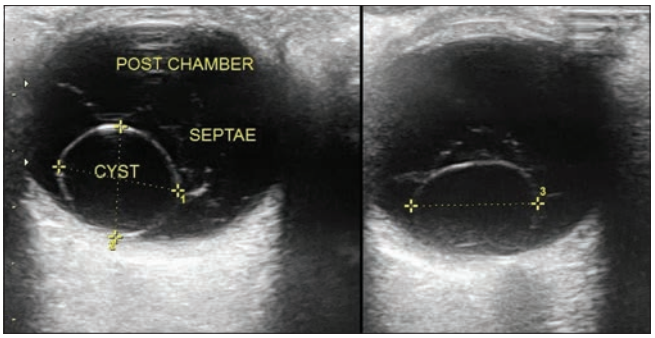


Figure 2: B-scan ultrasound showing a fixed vitreous cyst measuring 10.8 mm × 11.3 mm

Most of the idiopathic vitreous cysts which were reported earlier are pigmented and free floating in vitreous. However, in our case, an adult presented with a large vitreous cyst which was nonpigmented and fixed posteriorly. Such large, nontraumatic, idiopathic cysts have rarely been reported. Despite the size, the patient can be managed conservatively as the patient is asymptomatic. Intervention in the form of laser cystotomy or vitrectomy may be indicated if the patient develops any symptoms.

CONCLUSION

Primary fixed vitreous cyst is a rare entity. Our case documents a possibility of a large nonmobile vitreous cyst which can be kept under observation if the patient is asymptomatic.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Long-term linezolid: Unnerving the nerves?

ABSTRACT

It is well documented that systemic antimicrobials can cause ocular side effects. This becomes especially relevant in multidrug therapy where more than one drug can cause similar ocular side effect. We describe a case of progressive decrease in vision associated with linezolid therapy in a 17-year-old female patient, on treatment with the second-line anti-tuberculous drugs including linezolid, for multiple drug-resistant tuberculosis presented to us with painless progressive decrease in vision in both eyes. Color vision was defective and fundus examination revealed optic disc edema in both eyes. Since the patient was not on ethambutol and gave a history of peripheral neuropathy, linezolid-induced toxic optic neuropathy was suspected and linezolid dechallenge was done. Discontinuation of linezolid treatment resulted in marked improvement in visual acuity. Our report emphasizes the need for early detection of ocular side effects and how monitoring of visual function is imperative in patients on long-term linezolid treatment.

Keywords: Linezolid, optic neuropathy, ocular side effects

INTRODUCTION

Optic neuropathies are disorders of the optic nerve involving degeneration of the nerve. They are further classified into hereditary and acquired. Drug-induced optic neuropathy is of the toxic acquired type. Various anti-tubercular drugs are known to cause optic neuritis and optic neuropathy, the most common being ethambutol.

Linezolid, an oxazolidinone, has antibiotic activity against many important pathogens including multidrug-resistant tubercle bacillus and methicillin-resistant *Staphylococcus* and *Streptococcus*. We report a case of toxic optic neuropathy due to linezolid occurring in a patient who was on linezolid and other second-line drug therapy for multiple drug-resistant pulmonary tuberculosis (MDR-PTB). The incidence of this is not known yet.

CASE REPORT

A 17-year-old female presented to our outpatient department with painless progressive diminution of vision in both eyes for the last 15 days. Medical history was suggestive of MDR-TB on treatment with linezolid (600 mg/day), levofloxacin (750 mg/day), cycloserine (500 mg/day), ethionamide (500 mg/day), injection kanamycin (750 mg/day), clofazimine (100 mg/day), and pyridoxine (100 mg/day) for the past 6 months. All Category I drugs were discontinued in the 1st month due to resistance. On ocular examination, her distant visual acuity was counting fingers at 3 m in both eyes, not improving with pin hole, and near visual acuity was N18. Color vision was defective in both eyes (with Ishihara charts). Anterior-segment examination was unremarkable; pupils were 3 mm, round, regular, and reacting to light in both eyes (direct and indirect). There was no relative afferent pupillary defect. Both eye fundus examination revealed hyperemic disc with blurred margins [Figure 1]. Optical coherence tomography (OCT) revealed increased retinal nerve fiber layer (RNFL) thickness to 186 µm in both eyes [Figure 2]. Visual field evaluation by Humphrey field

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analyzer showed generalized depression in the right eye and sensory loss in the left eye corresponding to the disc edema [Figures 3 and 4]. Of all the medications the patient was on, linezolid is known to cause optic neuropathy. Further, the patient had a history of peripheral neuropathy 4 weeks before onset of ocular symptoms which was treated with oral pregabalin. The patient was diagnosed with linezolid-induced optic neuropathy. Linezolid was discontinued after opinion from the treating physician, and following that, over the next 2 weeks, the patient's unaided distant visual acuity improved to 6/9 in the right eye and 6/6 in the left eye and near visual acuity improved to N6. Color vision recovered and the patient's unaided visual acuity was restored to 6/6 for distance and N6 for near, in both eyes, after 1 month. Fundus examination revealed partial and complete resolution of right and left disc edema, respectively [Figures 5 and 6]. OCT demonstrated decrease in RNFL thickness to 159 µm in the right eye and 80 µm in the left eye [Figure 7] and the follow-up visual fields improved [Figures 8]; therefore, on the basis of Naranjo scale for adverse drug reaction, linezolid toxicity was concluded.

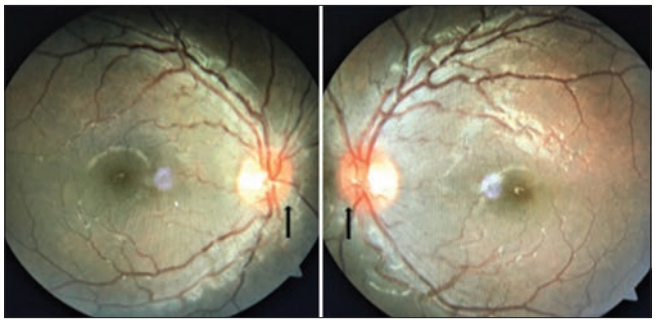


Figure 1: Both eyes showing optic disc edema

The patient was then started on para-aminosalicylic acid granules at the advice of the physician.

DISCUSSION

Optic neuropathies are disorders of the optic nerve involving degeneration of the nerve. They are further classified into hereditary and acquired. Drug-induced optic neuropathy is of the toxic acquired type. Toxic optic neuropathy has been associated with numerous compounds, including exposure to methanol, isoniazid, and ethambutol and deficiency of Vitamin B12, folate, and thiamine. It is characterized by gradual, progressive painless, bilaterally symmetric visual loss affecting central vision, and causing central or centrocecal scotoma.

MDR-TB is defined as resistance to at least rifampicin and isoniazid among the first-line anti-TB drugs. Linezolid acts by inhibiting protein synthesis and disrupting mitochondrial phosphorylation (binding to 16SrRNA) by preventing the formation of the ribosome complex that initiates it. Its unique binding site results in no cross-resistance with other drug classes; hence, linezolid is being increasingly used for the treatment of infections caused by multidrug-resistant Gram-positive bacteria. Linezolid is usually well tolerated with few adverse effects. Serious adverse reactions demanding withdrawal of the drug include myelosuppression, peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome.[1,2,3] Linezolid was approved by the FDA, based on the studies employing 28 days of administration.[4] There are several case reports of linezolid-induced optic or peripheral

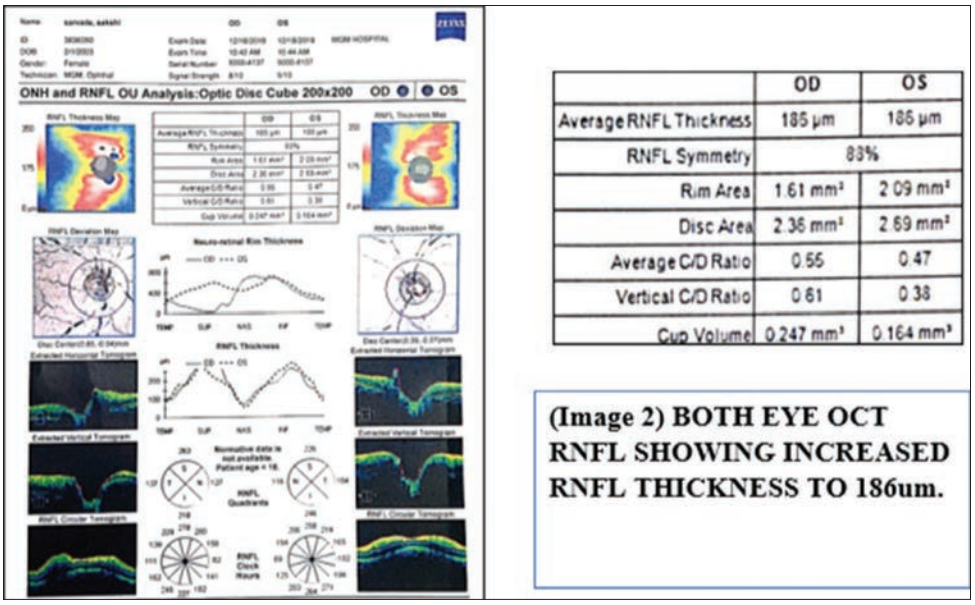


Figure 2: Optical coherence tomography retinal nerve fiber layer showing increased retinal nerve fiber layer thickness

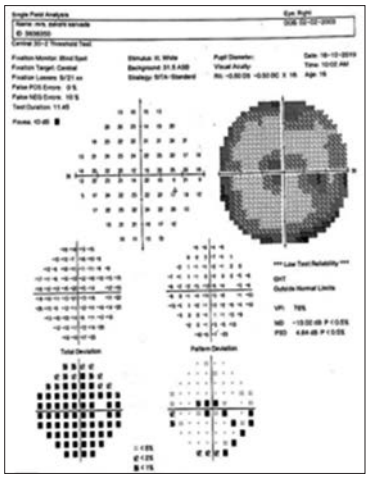


Figure 3: Right eye visual field showing generalized depression

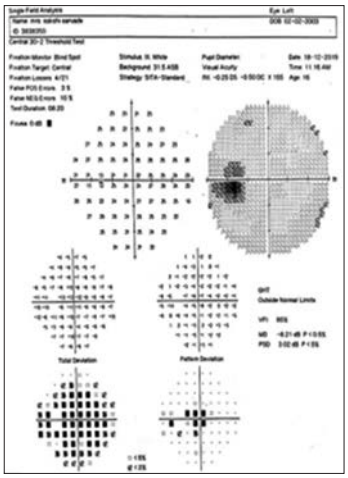


Figure 4: Left eye visual field showing minimal depression due to optic disc edema

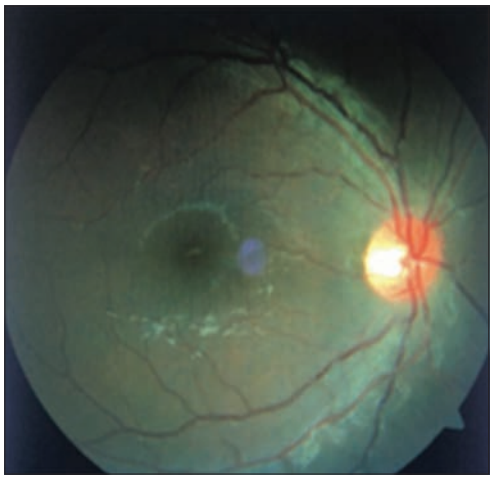


Figure 5: Right eye fundus photograph showing resolving optic disc edema



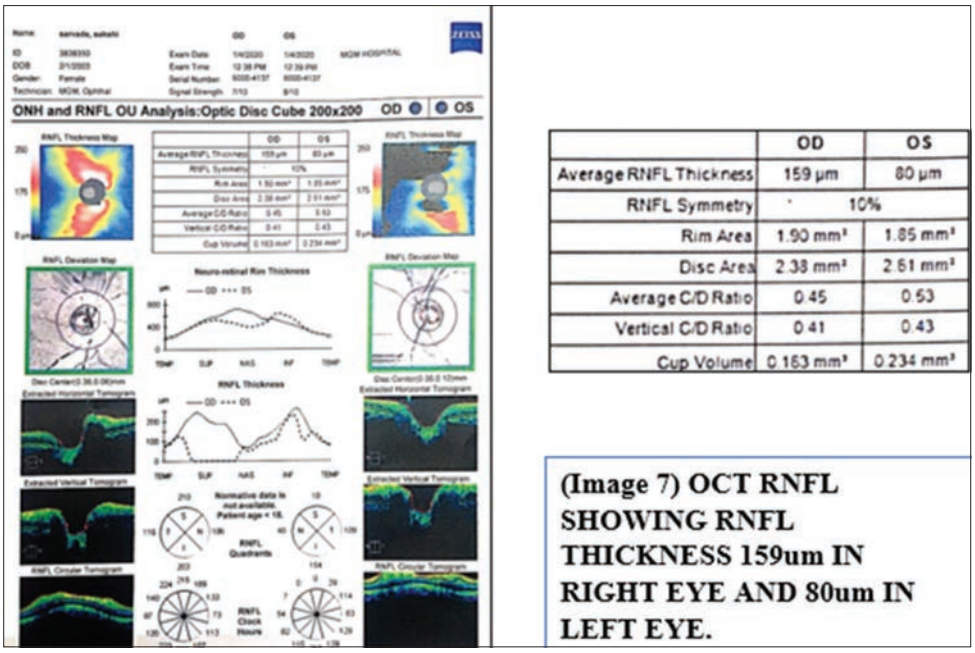
Figure 6: Left eye fundus photograph showing resolved disc edema

neuropathy in patients treated for a time period beyond 28 days.[5] Only two cases of toxic optic neuropathy have been reported following short-term linezolid treatment of 16 days.[6,7] Discontinuation of linezolid therapy resulted in improvement of the optic neuropathy with significant improvement in visual acuity within 1–8 months.[8]

Fundus picture can be varied, showing temporal pallor, disc edema, or essentially normal. Complete visual recovery has been reported in all cases except one.[7] Although nearly complete recovery has been reported in most such cases, the psychological effects of bilateral drastic visual loss can be devastating, therefore best avoided by careful monitoring and discontinuation of drug if needed. The most common indication for long-term linezolid therapy has been infection with methicillin-resistant Staphylococcus aureus but in our case, optic neuropathy occurred after using linezolid for 6 months at a dose of 600 mg per day for infection with *Mycobacterium tuberculosis*. Since our patient had a history of preceding peripheral neuropathy and her vision improved only after withdrawal of linezolid, she was diagnosed with linezolid-induced toxic neuropathy. There are limited data available regarding the efficacy and safety of linezolid in multidrug-resistant TB since it is always administered as part of combination therapy, but the recent PMDT guidelines, 2019 state it as a Group A drug in the treatment of MDR-TB.

CONCLUSION

With increasing emergence of MDR-TB, for which the treatment options are limited, physicians are compelled to resort to new drug therapies. Although ethambutol is the most common anti-tubercular drug implicated to cause toxic optic neuropathy, it is important to be aware that if patient is not on ethambutol, one must consider other drugs notorious for the same. With our country being rampantly affected



	OD	OS
Average RNFL Thickness	159 µm	80 µm
RNFL Symmetry	10%	
Rim Area	1.90 mm²	1.85 mm²
Disc Area	2.38 mm²	2.61 mm²
Average C/D Ratio	0.45	0.53
Vertical C/D Ratio	0.41	0.43
Cup Volume	0.163 mm³	0.234 mm³

Figure 7: Repeat optical coherence tomography retinal nerve fiber layer showing right eye resolving optic disc edema and left eye resolved optic disc edema

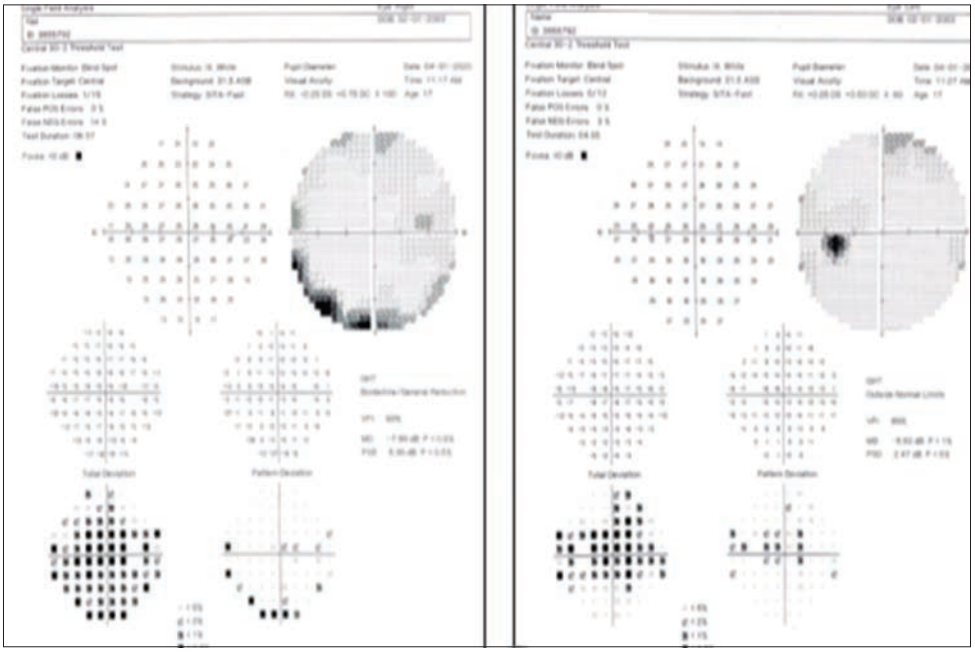


Figure 8: Repeat visual fields of both eyes showing improvement

with drug-resistant TB, where multiple drug therapy is the only option, this is even more a demand for being vigilant of side effects such as peripheral and optic neuropathy. Ophthalmologists and physicians must be aware that strict and regular monitoring of visual function is imperative in patients on long-term linezolid therapy. Also note that peripheral neuropathy should be recognized as an early sign of toxicity and due course of action must be taken to avoid the optic neuropathy which may follow, if linezolid is continued.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

The eyes show what the brain has: A case report on neuromyelitis optica

ABSTRACT

Neuromyelitis optica (NMO) is a rare autoimmune disease affecting nerves of the eyes and central nervous system. Etiology of NMO is yet to be completely defined. The purpose of this report is to bring to light one such unique case of NMO.

Keywords: Disc edema, neuromyelitis optica, neuroopthalmology

INTRODUCTION

Neuromyelitis optica (NMO) also referred to as Devic's disease and NMO spectrum disorders are a spectrum of inflammatory, autoimmune demyelinating disorders.[1] While the exact etiology of NMO remains unexplained, the disease is found to be associated with antibodies against aquaporin water channels. NMO can occur in any age, sex, or ethnicity; a certain predilection toward females and people of Asian or African descent has been observed.[2] The disease can adversely affect the spinal cord and optic nerve and may even prove life-threatening. Hence, it is important to obtain a complete understanding of the disorder to aid in better management of the same.

CASE REPORT

An 8-year-old girl presented to the ophthalmology outpatient department with the chief complaint of diminution of vision in both the eyes for the past 4 days. The diminution of vision was acute in onset, painless, progressive, and involved both peripheral and central fields of vision. There were no other ocular complaints. The patient also had complaints of fever, projectile vomiting, and headache for 4 days, for which she had been given symptomatic treatment. The parents gave no history of using spectacles, any ocular trauma or procedure. There was no history of any systemic illness. Her unaided distant visual acuity was hand movements close to the face with accurate projection of rays in both the eyes, which did not improve with the use of pinhole. Color vision and visual fields, however, could not be assessed. Pupils were bilaterally 6 mm, sluggishly reacting to light. Rest anterior segment examination was unremarkable. Intraocular pressures were 10 and 12 mmHg, respectively, on Perkin's applanation tonometer.

Dilated fundus examination showed bilateral disc edema with obscuration of all margins in both the eyes [Figures 1 and 2]. Blood vessels were dilated and telangiectatic. However, no collaterals were seen. There were no peripapillary hemorrhages seen. Blood tests including blood sugar levels, serum homocysteine, erythrocyte sedimentation rate, and c-reactive protein were normal. A lumbar puncture was carried out and cerebrospinal fluid (CSF) was studied. CSF IgG was 3.48, while the rest was within the normal limits. Magnetic resonance imaging of the brain

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plain and contrast studies were carried. Multiple T2 and fluid-attenuated inversion recovery hypersignal intensity was noted in the bilateral parietal and right frontal region at the corticosubcortical level. It was associated with gyral enhancement in the bilateral frontoparietal region [Figure 3]. Degenerative disorders were suspected and further blood testing was carried out. Antinuclear antibodies, p-antineutrophil cytoplasmic antibodies (ANCA), and c-ANCA were negative. Aquaporin-4 antibodies were negative, but myelin oligodendrocyte glycoprotein (MOG) antibodies were positive, thus supporting the diagnosis of NMO.

Corticosteroids are the mainstay treatment for the acute phase of the disease. The patient was started on intravenous methylprednisolone at a dose of 1 mg/kg/day for 3 days and then subsequently shifted to oral prednisolone 40 mg/day for 4 weeks. The visual acuity was reassessed every 2 days. The patient was also given long-term care including medical rehabilitation, management of anxiety and depression, and symptomatic treatment for gastrointestinal problems, pain, etc.

On the 10th day follow-up, best-corrected visual acuity was same in the right eye (RE) but improved to finger counting at 2 m in the left eye (LE). After 1 month, the LE visual acuity further improved to 6/60. Fundus examination showed a pale, atrophic disc in the RE [Figure 4], whereas the LE showed resolution of disc edema [Figure 5].

This patient was also treated with 50 mg twice daily dose of azathioprine as maintenance therapy to prevent relapse and no relapse episodes have been noticed till date.

DISCUSSION

NMO, also known as Devic's disease, is an autoimmune,



Figure 1: Fundus picture of the right eye showing disc edema with a blurring of all disc margins



Figure 2: Fundus picture of the left eye showing disc edema with a blurring of all disc margins

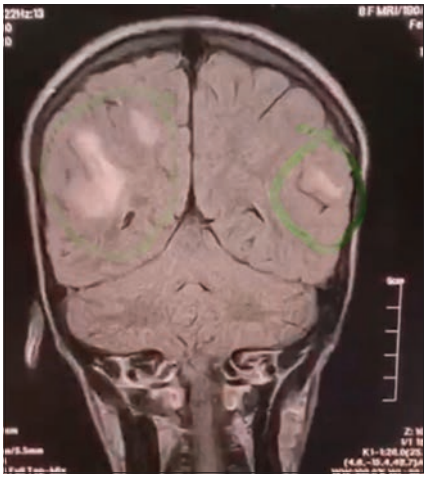


Figure 3: Magnetic resonance imaging of the brain showing multiple hyperintensities noted in the bilateral parietal and right frontal region



Figure 4: Fundus picture of the right eye on day 10 showing pale, atrophic optic disc

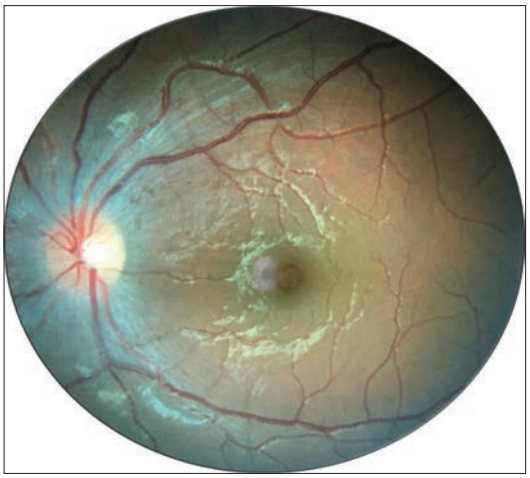


Figure 5: Fundus picture of the left eye on day 10 showing resolving disc edema

immunological disease with formation of antibodies against the central nervous system.[3] These antibodies cause demyelination of the optic nerve and spinal cord giving rise to the following distinctive features:

Optic neuritis that presents with acute optic disc swelling and can further progress to optic atrophy.

There is decreased visual acuity, abnormalities in color vision, and reduced field of vision.

A relative afferent pupillary defect might be present.

The spinal cord involvement leads to hemiparesis or even tetraparesis with bladder involvement.

NMO usually has a chronic and relapsing course with recurrent attacks of transverse myelitis or optic neuritis which are usually followed by only partial recovery.

Dyspnea may also be present.

Other clinical symptoms include brain stem symptom, posterior reversible encephalopathy syndrome, coma, hypothalamic dysfunction, depression, cognitive disorders, psychiatric symptoms, and abnormal endocrinopathy.[4]

NMO is a rare syndrome accounting for $<1\%$ of demyelinating disease. A variable incidence has been reported ranging from 0.05 to 4.4 per 100,000.[4] The typical clinical manifestations of NMO, mainly optic neuritis and transverse myelitis, can occur simultaneously or separated by a variable amount of time. While in 90% of cases, the presentations are polyphasic, 10% monophasic presentation has also been reported.

The presence of antibodies proves the definitive diagnosis of NMO. The aquaporin-4 (AQP4) immunoglobulins are detected in about 60%–90% of patients who meet the clinical and radiological criteria of NMO. However, in patients who are AQP4 antibodies negative, it is imperative to check MOG antibodies.[5] This patient was negative for AQP4 antibodies, but positive for MOG antibodies. Patients with MOG antibodies are more likely to have a spinal involvement and thus likely to have a severe disease course.

The differential diagnoses for NMO include multiple sclerosis (MS), acute disseminated encephalomyelitis, idiopathic acute transverse myelitis, and systemic lupus erythematosus. Although NMO was previously thought to be a variant of MS, it has now been recognized as a separate disease entity.[6] Distinguishing NMO from MS is very important as presentation, pathogenesis, progression, treatment, and prognosis of both diseases are different.

CONCLUSION

Although NMO is a rare disorder, it is important to study the disease pathogenesis in details. Rapid diagnosis and early initiation of aggressive immunosuppressive treatment are essential in most NMO cases. The chances of recurrence of the disease are $>90\%$ and these subsequent attacks can prove to be life-threatening if lesions involve the spinal cord or the brain stem by affecting the respiratory centers. While NMO is a rare disorder, cases with bilateral optic neuritis should be evaluated in detail, and the possibility of NMO should be taken into account in the differential diagnosis to ensure timely diagnosis and effective management. This not only improves the life expectancy, but may also improve the quality of life of the patient by reducing the number of relapses.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

A case of bilateral sequential optic neuropathy in a young adult post hemodialysis

ABSTRACT

Ischemic optic neuropathy is a very rare but well-known complication following hemodialysis in patients with chronic kidney disease, It can be potentially blinding when involving both optic nerves and there is no effective established treatment available so far. If involvement of one eye is detected earlier, a multidisciplinary approach and efforts directed at controlling risk factors such as anemia and hypotension will go a long way in preventing the involvement of other eye in young individuals. We report a case of posterior ischemic optic neuropathy in the right eye with recovery of vision but persistent color vision deficit with recent-onset nonarteritic anterior ischemic optic neuropathy in the left eye, which has not been reported so far.

Keywords: Anemia, hemodialysis, hypotension, ischemic optic neuropathy, visual loss

INTRODUCTION

As described in the literature, anterior ischemic optic neuropathy (AION) primarily involves interference with the posterior ciliary arterial blood supply to the prelaminar optic nerve.[1] This might be brought about by decreased blood delivery, increased resistance to blood supply, or low blood oxygen-carrying capacity.[2] Patients with chronic kidney disease have comorbidities such as hypertension, atherosclerosis, and anemia, which predispose them to ischemic optic neuropathy. An association between acute ischemic optic neuropathy and hypotension during general surgeries, cardiopulmonary bypass, has been documented in various case reports. Hemodialysis-associated hypotension has also been proven as a significant cause of ischemic optic neuropathy. We report one such unique case of old posterior ischemic optic neuropathy (PION) in one eye with sequential involvement of other eye in the form of nonarteritic anterior ischemic optic neuropathy (NAAION) in a young adult male on hemodialysis, which has not been reported before.

CASE REPORT

A 31-year-old male patient admitted in the medicine department was referred to our outpatient department with a history of sudden-onset painless decrease in vision in the left eye 15 days before following a session of hemodialysis. There were no history of redness, photophobia, and flashes/floaters; no associated pain on eye movements; and no history of headache, and vomiting. There was a history of a similar episode of diminution of vision in the right eye a year back with complete recovery in few weeks. The patient

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was a case of bilateral chronic kidney disease for the past 3 years. He was on dialysis for 2 years, thrice weekly, and on antihypertensive medications. No other significant past or family history was present.

Ocular examination revealed a visual acuity of 20/20 in the right eye and counting fingers at 3 m in the left eye, not improving with pinhole with Snellen's chart. Pupillary evaluation showed a briskly reacting pupil to light in the right eye and sluggishly reacting pupil in the left eye. There was Grade 1 relative afferent pupillary defect in the left eye. There was no light near dissociation. Extraocular movements were full in both eyes. There was no pain associated with eye movements. Color vision recorded with the Ishihara pseudoisochromatic chart was 1/16 in the right eye and 0/16 in the left eye. Intraocular pressure was within normal range in both eyes. Fundus examination with slit-lamp biomicroscopy of the right eye showed 0.3:1 cup-by-disc ratio with mild temporal pallor [Figure 1]. The left eye showed 0.3:1 cup-by-disc ratio, sectoral inferior pallid disc edema [Figure 2]. There was no evidence of any hemorrhages. Foveal reflex was present in both eyes, with the rest of the retinal examination being normal. Humphrey visual field automated perimetry 30-2 Swedish Interactive Threshold Algorithm (SITA) standard was done. The right eye showed peripheral constriction of fields on the nasal side [Figure 3] and the left eye showed incomplete biarcuate defects [Figure 4]. The patient was diagnosed as NAAION in the left eye and PION in the right eye based on the above findings. His blood reports showed high serum creatinine (9.3 mg/dL), serum urea (66.5 mg/dL), and blood urea nitrogen (31.07 mg/dL). His hemoglobin was 8.3 mg/dL, along with a low red blood cell count. Computed tomography scan brain with orbit was done, in which no significant abnormality was noted. The patient was advised to avoid antihypertensive medications in the evening to avoid nocturnal hypotension, and medications for correction of anemia were prescribed. The patient was followed up after 2 months. The visual acuity was the same and color vision was 1/16 in the right eye and 1/16 (from 0/16 previously) in the left eye. On dilated fundus examination, the left eye showed inferotemporal disc pallor with resolving disc edema.



Figure 1: Fundus photo of Right eye showing mild temporal pallor of disc



Figure 2: Fundus photo of Left eye showing inferior pallid disc oedema

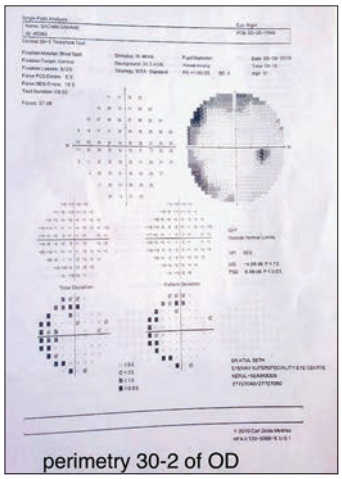


Figure 3: Perimetry 30-2 of Right eye showing nasal constricted field

DISCUSSION

Optic nerve disease has been reported in patients with renal dysfunction. It was presumed to be due to uremia and hence toxic optic neuropathy. The incidence of optic neuropathy of renal failure has not been determined. Sajjad *et al*. observed four patients on dialysis with optic neuropathy. Each patient had long-standing renal failure and its sequelae of anemia and hypertension. The immediate causes of ischemia were hypotension in 1, severe anemia in 1, and generalized atherosclerosis in two patients.[3] Optic neuropathy is a well-known complication of renal failure/dialysis. A neurotoxic type of optic neuropathy in uremic

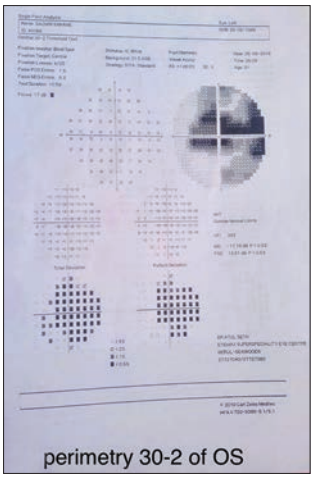


Figure 4: Perimetry 30-2 of Right eye showing incomplete biarcuate defects, denser superiorly

patients with a serum urea nitrogen level of >35.7 mg/dl was reported by Knox *et al*., who implicated hypertension and anemia as well as a raised serum urea nitrogen. Medical management with hemodialysis was followed by improvement of vision in four of their patients.[4] Hamad *et al*. described a similar type of optic neuropathy in patients maintained on dialysis.[5] Karen *et al*. reported a case of AION as a result of hemodialysis-associated hypotension (decreased blood delivery).[6] The pathogenesis of AION primarily involves interference with the posterior ciliary artery blood supply to the prelaminar optic nerve.[7] This might be brought about by decreased blood delivery, increased resistance to blood supply, or low blood oxygen-carrying capacity.[8]

Uremic patients may often have coexisting pathology such as hypertension, atherosclerosis (increased resistance), and anemia (low blood oxygen-carrying capacity), predisposing them to ischemic optic neuropathy.[3] Systemic steroids have often been the mode of therapy in AION. However, there is no strong evidence that favors their use. The rationale for the use of steroids in NAAION comes from the late 1960s that steroids would decrease capillary permeability, thereby inducing faster resolution of disc edema and this would reduce compression of capillaries in the optic nerve head and improve blood flow, restoring the function of surviving, but nonfunctioning, ischemic axons.[9] Our patient had dialysis-associated hypotension and anemia, resulting in sudden painless loss of vision as a presentation of AION and PION, which was the diagnosis made by clinical correlation and perimetry findings. The patient improved along with the medical management of hypotension and anemia, which was seen on further follow-up visits. In conclusion, with the expansion of the demand for renal replacement therapy, an increasing number of patients are receiving dialysis, often in the presence of multiple pathologies, including diabetes, generalized atherosclerosis, and hypertension.[3] By identifying the risk factors and by ambulatory monitoring of blood pressure during dialysis, the occurrence of ischemic optic neuropathy can be prevented.

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

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Case Report

Superficial variant of granular corneal dystrophy-description of four cases

ABSTRACT

In this case series, we describe four members of a family with the phenotype of superficial variant of granular corneal dystrophy (GCD). The complete description of cases, clinical photographs, anterior segment optical coherence tomography and discussion of treatment outcome have been highlighted. The common symptom for which the patients sought medical attention was blurring of vision. Typical corneal lesions were fluffy, white, too numerous to count, and in the most superficial part of corneal stroma. In all cases, the lesions recurred in spite of the different modes of the initial treatment. The recurrent lesions were also abundant but superficial in location and were managed successfully. Based on anterior segment optical coherence tomography and clinical findings, we thus describe a superficial variant of GCD occuring in three generations of a family with onset before 6 years of age and which recurred even after the best of clearance.

Keywords: Alcohol epitheliectomy, granular corneal dystrophy, phototherapeutic keratectomy, superficial variant

INTRODUCTION

Classic granular corneal dystrophy (GCD) was first described by Groenouw in 1988.[1] Its heredity is autosomal dominant, but a sporadic form had also been seen. Sajjadi and Javadi[2] described 17 cases of superficial variant of GCD. This dystrophy differed from classic GCD in the following ways: (1) age of decreased visual acuity (always in the mid to late first decade), (2) earlier need for surgical intervention, (3) superficial location of lesions, and (4) abundance of lesions. Whereas in classic GCD, the disease progresses very slowly and patients will have good vision in the first and second decades, and surgical intervention may not be needed until the fourth or fifth decades of life.[3]

DESCRIPTION OF CASES

Case 1

A 6-year-old boy was referred for the second opinion regarding management. He had defective vision and glare since few months. Ocular history was unremarkable, and there was no history of consanguinity in the family. There was a history of similar illness in the family which is described in the family tree in Figure 1. On ocular examination, his visual acuity (VA) was 20/200 in RE and 20/80 in LE. Slit-lamp examination showed multiple superficial opacities with a geographic pattern in the most superficial part of cornea [Figure 2]. The underlying stroma was clear which was confirmed by Anterior Segment OCT [Figure 3]. Remaining ocular examination was unremarkable. He underwent alcohol epitheliectomy with superficial keratectomy under general anesthesia first in RE followed by LE. He maintained 20/25 VA both eyes till 3-year postoperative. However, after 3 years, he

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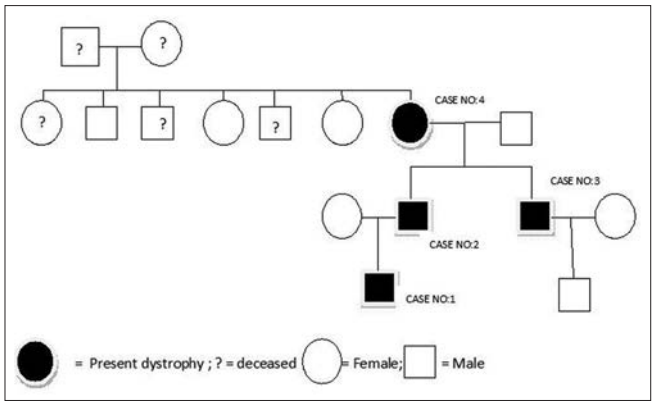


Figure 1: Chart depicting the Family tree

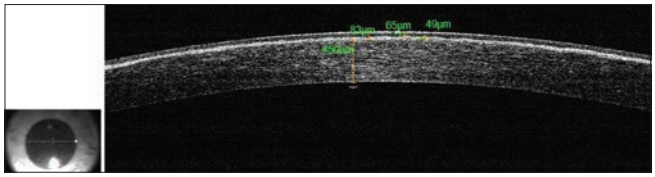


Figure 3: Anterior Segment (AS) optical coherence tomography of case 1 showing hyper-reflective superficial lesions with clear underlying stroma

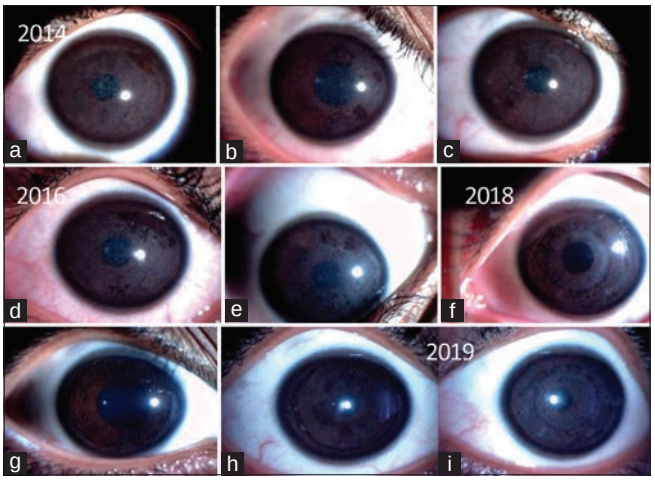


Figure 2: Diffuse slit-lamp photomicrographs of case 1: Recurrence of superficial dystrophy following alcohol epitheliectomy (a-e); clearance centrally following phototherapeutic keratectomy (f and g); recurrence following phototherapeutic keratectomy (h and i)

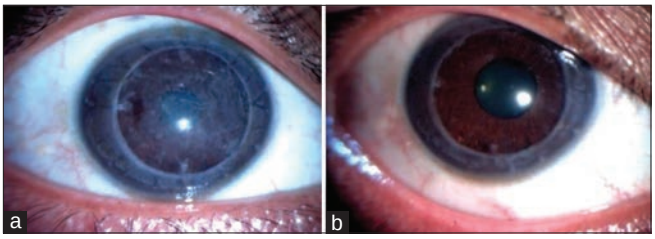


Figure 4: (a) and clear graft RE following phototherapeutic keratectomy (b). RE: Right eye, LE: Left eye

came with recurrence and blurring of vision LE > RE. Since his parents opted for phototherapeutic keratectomy (PTK), he underwent the same first in LE followed by RE [Figure 2f and g]. After 2 years, he was seen with recurrence [Figure 2h and i] but was maintaining a corrected VA of 20/32.

Case 2

Case 2 was a 40-year-old diabetic male who is the father of case 1. Ocular history revealed defective vision which had started at the first decade. He had undergone penetrating keratoplasty previously and he had gross visual disability at the time of visit. Ocular examination showed graft recurrence LE > RE and VA was 20/160 in RE and 20/500 in LE. He underwent repeat penetrating keratoplasty with intraocular lens (IOL) LE and was maintaining clear graft and VA was 20/40 LE for 4 years. Unfortunately, he had traumatic graft dehiscence with IOL extrusion LE which was managed by graft resuturing and anterior vitrectomy and his VA drastically was reduced to HM. By that time, he was visually handicapped since the graft recurrences in his RE have grossly reduced his vision to CF 1 M [Figure 4a]. PTK was done in May 2018 in his RE and for the past two years, his graft is clear in the centre [Figure 4b) and is enjoying an uncorrected VAof 20/63. PTK was done since the anterior segment OCT RE showed superficial lesions[Figure 5] amenable for the same.

Case 3

Case 3 was a 35-year-old male, brother of case 2 and paternal uncle of case 1. He came to see us in 2014. He gave a history of bilateral defective vision since early childhood. He had undergone penetrating keratoplasty LE 15 years back. On presentation, his VA in RE was CF 3 M and 20/200 in LE with graft recurrence [Figure 6a]. He wanted PKP in RE (he had undergone PTK multiple times elsewhere). After RE penetrating keratoplasty, he is under regular follow-up and his RE graft is maintaining clarity with uncorrected VA (UCVA) of 20/32 [Figure 6b].

Case 4

A 69-year-old homemaker (mother of case 2 and case 3 and paternal grandmother of case 1) was seen in our outpatient department in 2016. She gave a history of blurred vision which had started since very early years of life. She had undergone penetrating keratoplasty with IOL BE 25 years back which was repeated in RE 10 years and in LE 15 years back, respectively. On presentation, her VA was CF 2 M RE and CFCF LE. She had graft recurrence in RE and disorganized anterior segment in LE [Figure 7a]. By the time, she came to us, she was aware of all the modalities of treatments for her eye condition! She wanted to try PTK in RE and after explaining all the risks and making her aware about the

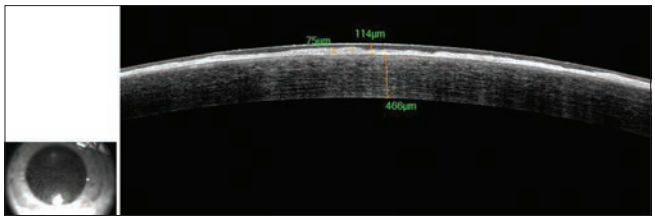


Figure 5: Anterior segment optical coherence tomography of RE of case 2 showing hyper-reflective line depicting the superficial lesions below epithelium and the clear stroma underneath. RE: Right eye

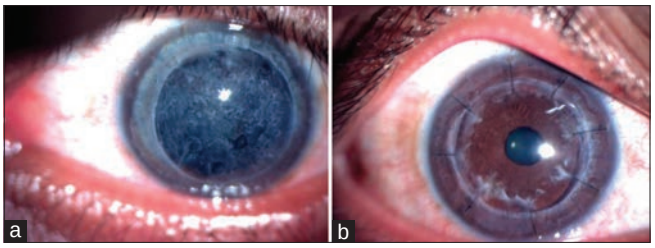


Figure 6: Slit-lamp photographs of case 3 showing recurrence in RE (a) and clear graft in LE (b). RE: Right eye, LE: Left eye

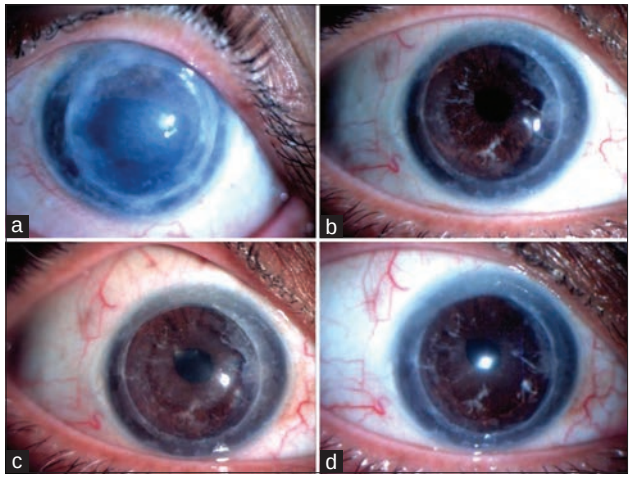


Figure 7: Slit-lamp photographs of case 4 showing a failed graft LE (a); graft cleared of recurrence following phototherapeutic keratectomy RE (b); recurrence following phototherapeutic keratectomy in RE (c); clear graft following second phototherapeutic keratectomy (d). RE: Right eye, LE: Left eye

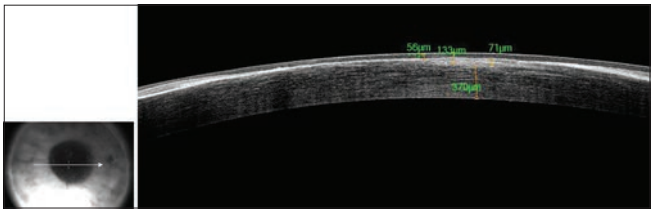


Figure 8: Anterior segment optical coherence tomography of case 4 showing clearly delineated superficial corneal deposits

recurrences which can happen after the procedure PTK was done in RE. Her visual axis was cleared following PTK [Figure 7b] and she had UCVA 20/15. After 3 years, her vision dropped to 20/80 due to recurrence of lesions [Figure 7c] a second-time PTK was done [Figure 7d] after checking the depth of the lesion in AS OCT [Figure 8] and is having UCVA 20/15 for 1 year.

Comment

The corneal opacities in classic granular dystrophy have an early onset, but vision is not impaired at this stage of development, and the patient experiences no discomfort. Corneal deposits in classic GCD are mainly located in the axial portion of the cornea and are small, discrete, demarcated grayish-white opacities in the stroma. The clinical features in our patients are similar to those previously described in the superficial variant of GCD.[2] The lesions were fluffy, snowflake: like, white, and always too numerous to count. The course of the disease in this variant is aggressive, with patients becoming symptomatic at an earlier age.[4] Four persons affected with this disorder have been identified in three generations. All the four patients had very early onset of lesions and vision was affected before 5–6 years.

Mashima *et al*. described a novel R124 L mutation of the BIGH3 gene which was associated in a family with a superficial variant of GCD.[5] This mutation causes a severe form of superficial variant of GCD producing abnormal keratoepithelin between the epithelium and the Bowman's layer, and thus, there are clinical similarities to Reis-Bucklers corneal dystrophy (RBCD). Good surgical results with limited instrumentation from alcohol epitheliectomy,[6] superficial keratectomy, excimer laser PTK[7] make recognition of this variant dystrophy important. These procedures do not require a donor tissue and can be repeated. Although PKP is effective in the management of such eyes, the recurrence of dystrophy in the graft happens.

CONCLUSION

This family has a superficial variant of GCD or true RBCD. The term superficial variant of GCD used in this article is based on AS OCT and clinical findings. The ultra-high-resolution OCT provided clear delineation of corneal anatomic features and pathologic corneal deposits in most cases. The characteristics and depth of these deposits are illustrated and can be localized to specific layers of the cornea.[8]

Molecular genetic analysis of affected persons is not done which would have given the information regarding the mutation in the family.

This report is lacking a histopathology report since it was done 4 years before but could not retrieve the slides and report.

The lesions which recurred later were managed by PTK, and so, specimen for histopathology was not available.

None of our patients had recurrent erosions which are seen in RBCD. Granular material that is more anterior will give rise to erosions which is true to RBCD. The affected persons in this family have more clinical similarities to GCD.

Declaration of patient consent

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Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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When iron hits; iris safeguards, lens surrenders

Foreign body (FB) penetrating the eye to a variable depth is a frequently observed problem in the ophthalmology outpatient department. This article narrates two cases with metallic intraocular FB (IOFB) of which one was safely removed, while the other was referred to a higher center.

Case 1 [Figure 1] shows a 25 year-old-male laborer who presented with diminished vision, pain, redness, and watering in the left eye (LE) after having injury while grinding an iron rod 1 day back. Best-corrected visual acuity was finger-count 5 m. Slit-lamp examination (SLE) revealed diffuse conjunctival congestion and self-sealed (Seidel's negative) corneal tear with the iron particle in the anterior chamber (AC). AC showed Grade-4 flare and cells. The iron particle was adherent to iris by fibrous membrane. Fortunately, the lens was clear with an intact anterior capsule. Fundoscopy and B-scan revealed a normal posterior segment. Orbital computed tomogarphy (CT) ruled out any other FB or damage. Inside OT, under sub-tenons block, the iron particle was mobilized after breaking surrounding adhesions and oriented such that it could be taken out from the same entry without the creation of another port. Copious viscoelastic was used to avoid collateral damage to the lens and endothelium. The sharp iron particle (4 mm × 6 mm) was extracted out and corneal tear was repaired with (10-0) nylon sutures. Uncorrected visual acuity at postoperative day-7 was 6/12 [Figure 2].

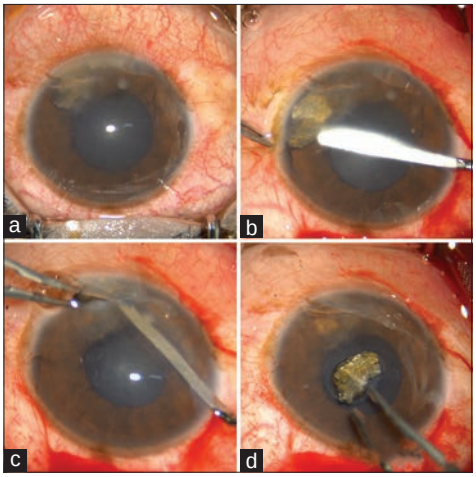


Figure 1: Intraoperative photographs. (a) Iron particle adherent to iris. (b) Iron particle being mobilized and re-oriented with a spatula after adhesiolysis. (c) Iron particle being extracted out from the same entry wound. (d) Iron particle being shown after extraction

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Case 2 [Figure 3] illustrates a poor 45-year-old-male presented with diminished vision and pain in LE after getting injured while hammering a chisel 6 h ago. Visual acuity was an accurate perception of light but an inaccurate projection of rays. SLE revealed diffuse conjunctival congestion and full-thickness (Seidel's positive) vertical corneal tear involving visual axis with tiny FB particles lying at the edge. Shallow AC, traumatic mydriasis, sphincter tear, and traumatic cataract were noted. Close examination revealed incomplete bisection of the lens which was suggestive of FB having penetrated into the vitreous cavity. X-ray orbit showed the presence of intra-ocular radio-opaque particle. B-scan was deferred because of poor wound integrity. Noncontrast head CT orbit was advised, but the patient refused. Careful SLE helped catching the trajectory of FB and thus timely referral of the patient to a higher center.

During penetrating trauma, the direction and site of impact, along with the mass and velocity of the FB, determines its final position inside the eye. Objects with lower mass (usually

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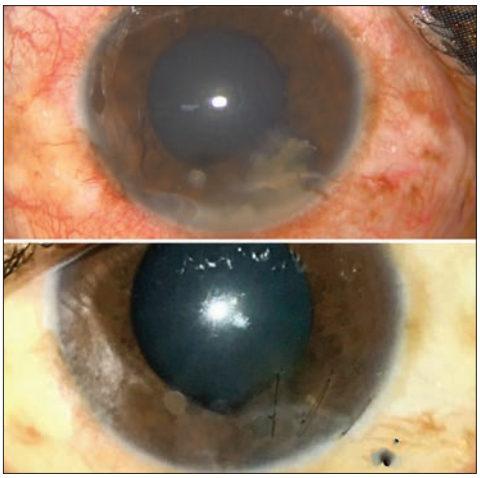


Figure 2: Slit-lamp photograph: Above - Preoperative: Diffuse conjunctival congestion with self-sealed corneal tear and iron particle with surrounding exudative membrane in anterior chamber. Below: postoperative day-7: Quiet eye with intact corneal suture and well-formed anterior chamber

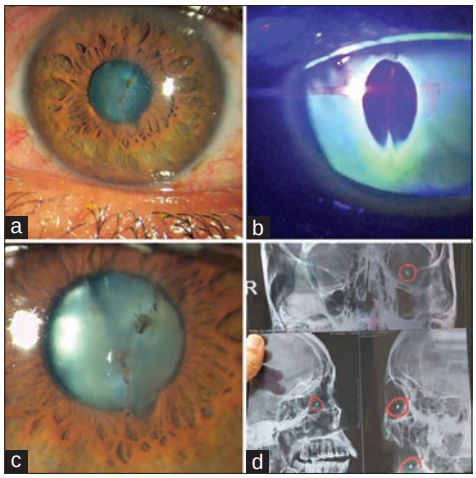


Figure 3: (a) Slit-lamp photograph at × 10: Vertical full thickness corneal tear and traumatic cataract. (b) Positive Siedel's test confirming aqueous leak. (c) Slit-lamp photograph at × 25: Showing corneal foreign body, sphincter tear and partially bisected lens. (d) Orbital X-ray: Revealing presence of metallic foreign body (in red circle)

nonmetallic) and lesser velocity seem to remain in AC. In contrast, objects with greater mass (metallic) come to lie more commonly in the posterior segment.[1] Such cases occur when there is splashing of the FB, commonly seen during drilling.[2]

Orbital X-ray is helpful to detect radio-opaque FBs, but CT-Scan is the preferred modality as it provides more information such as size, shape, and localization of the FB. Magnetic resonance imaging is not used for metallic-IOFB as it can dislodge the FB and cause further destruction. B-scan is usually avoided in open globe injuries. Ultrasound biomicroscopy is used when FB in the angle is suspected.[3]

Siderosis bulbi is a degenerative change caused by Iron FB, occuring 2 months to 2 years after injury where iron undergoes electrolytic dissociation producing ions which combine with intracellular proteins and cause degeneration.[4]

Prompt management including timely removal of FB is of paramount importance, but wearing protective eye gear is the first step in avoiding such injuries.[5]

Declaration of patient consent

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Conflicts of interest

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Eye to Eye Fundus Imaging with Ophthalmic Wand - Anytime! Anywhere!!

ABSTRACT

Conventionally, fundus camera is the only source for taking retinal images. With the advent of smartphones, fundus photography has become more portable, simpler, cheaper, and easier. Various techniques of fundus imaging with smartphones were put forth in the last decade. Senior ophthalmologists always prefer using a direct ophthalmoscope (DO) for viewing the fundus. DO has the advantage of viewing magnified images giving no scope in missing findings. We illustrate the use of a smartphone and a DO in recording patient's facial details, distant direct ophthalmoscopy apart from taking images of normal/pathological lesions of the optic disc, vessels, and retina in the form of a videograph or photograph. This technique is extremely useful for training purposes, bedside-imaging as in intensive care unit/wards, in remote areas such as camps, creating patient awareness, counseling, monitoring the progression, documentation, sharing, and cross consultation. These advantages are being utilized in our institute since 2014.

Keywords: Direct ophthalmoscope, fundus imaging in COVID times, smartphone, smartphone-based fundus imaging, smartphone fundoscopy, smartphone ophthalmoscopy

Clinical photographs are important in the understanding of any condition. Conventionally, fundus camera is used in imaging the posterior segment. It is always expensive, needs space to accommodate, and not easily portable. It cannot be afforded by many of the private ophthalmologists. The advent of smartphones had come to this rescue. Various techniques of imaging with smartphones were put forth in the last decade.[1,2] We illustrate the use of a smartphone (iPhone 5, Apple Inc.,) and a direct ophthalmoscope (DO; Neitz BX α, Neitz instruments, Tokyo) for imaging the eye in undilated or dilated pupils [Figure 1a]. The technique avoids proximity of the examiner to the patient, unlike using a routine DO, which is especially useful in this COVID era [Figure 2a - c].

TECHNIQUE

The light source from the DO is turned on and it illuminates the retina. The smartphone camera is opened in video/camera mode and the camera eye is placed in contact to the viewing aperture of the DO. Any brand model Smartphone or DO can be employed for using this technique. The examiner uses both of his/her hands to stabilize the smartphone and DO unit [Figure 1c]. The fingers of the nondominant hand can be used to retract the eyelids for better exposure [Figure 1b]. The DO-Smartphone unit [Figure 1c] can be used for viewing distant direct ophthalmoscopy when held 30–40 cm from the eye [Figure 3]. The patient's face details also can be captured [Figure 3a]. As the illumination is brought near to the patient's eye, the retina is visualized on the smartphone screen. The examination is then done as with a routine DO

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Figure 1: Technique of imaging. (a) A smartphone and a direct ophthalmoscope are required. (b) Smartphone- direct ophthalmoscope unit utilization in capturing images. (c) Side view of the technique of holding the smartphone camera eye in contact to the viewing aperture of the direct ophthalmoscope



Figure 2: Uses of the Smartphone- direct ophthalmoscope imaging technique. (a) Avoids examiner's proximity to the patient. (b) Useful in examining intensive care unit patients. (c) Imaging in camps. (d) Patient education



Figure 3: Distant direct ophthalmoscopy. (a) Can capture the patient's facial details along with the red-reflex in both eyes. (b) Red reflex of the right eye. (c) Red reflex of the left eye

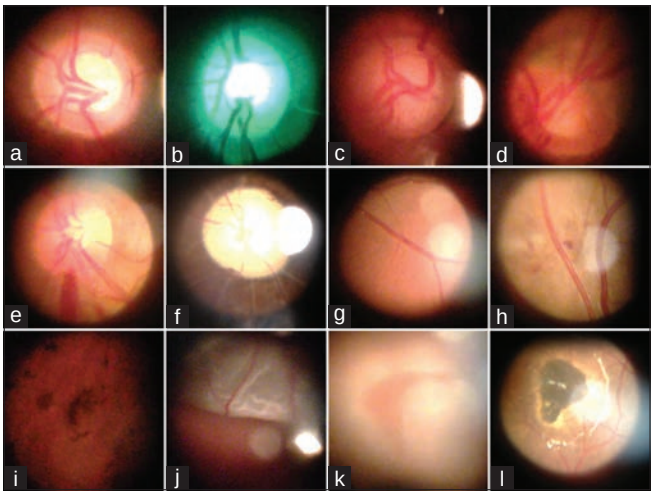


Figure 4: Clinical pictures of the optic disc and retina captured with our technique. (a) Normal optic disc with healthy NRR. (b) Utility of a red-free image. (c) Glaucomatous optic atrophy with loss of NRR. (d) Torsional disc. (e) Optic disc hemorrhage. (f) Optic disc pallor secondary to CRAO. (g) A-V crossing. (h) Microaneurysm (i) Bony spicules in RP (j) Retinal detachment (k) Horse-shoe tear noted in the RD (l) Chorioretinal scar

in the order of visualizing the optic disc first and macula last. During the examination, necessary photographs can be captured simultaneously from the recording video or extracted later as screenshots from the recorded video. The audio of the examiner explaining the lesions can also be utilized for training purpose. The imaging helps in viewing, recording, and documenting the fundus details like cup: disc ratio, appearance with red-free filter, venous pulsations, A-V crossing changes, background retina, and related pathologies [Figure 4]. The imaging can also be done in lying position, thus useful in bedside imaging as in medical ward/intensive care unit/comatose patients [Figure 2a and b], in remote areas like camps [Figure 2c], for patient education [Figure 2d], cross-consultation and training purpose.

We conclude that smartphone imaging with DO without the need of any adapter or lens is a simple, quick, and cost-effective technique of acquiring magnified fundus images anytime and anywhere.

Declaration of patient consent

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Dr. Charles Kelman: The Saxophone Player In Ophthalmologist's Mask

Can music attract medicine graduates to pursue a career in ophthalmology? Well, there is a famous American ophthalmologist who will vehemently say yes to that. He would also tell you that it is not because there is anything musical about ophthalmology, but just because it would give him the most flexible hours leaving him lots of free time to pursue his true passion which was music.[1] All he wanted in life was to be a great musician and saxophone player. He just wanted to be that star on the stage playing to the audience and basking in the applause. But fate had other plans for him. As a teenager, he was caught red-handed by his father at 2.00 a. m. in the night with his beloved sax in hand trying to run away from home so as to join Louis Prima's band. Taking the saxophone away from the 16-year-old, his father said: "You can be a singer, you can be a composer, you can be a songwriter, you can play with bands, you can do whatever you want. However, first you will be a doctor."[2] The boy did exactly that. With his head full of music and sax in hand, he joined medical school with the intention to make it a side story, while he pursued his true passion. However, the affliction of his father with cancer and subsequent death from it spurred him on, and he graduated in time.[1] After graduation when it was time to choose a specialty, he chose ophthalmology for the sole reason already mentioned. It proved to be the right decision for him as he could spend hours and hours writing and rehearsing pop songs. The young doctor struck gold when he approached Chancellor records with a pop song written and sung by him. The studio head liked it so much so that the young man was allowed to record the song himself. Nervous about the reaction from his colleagues, he recorded under a false name, Kerry Adams. Kerry Adams shot to fame as the song (Telephone Numbers) became a box office hit. He was elated. His life's dream had come true, and his career was made. Music and entertainment would be his life with medicine playing the sidekick. However, it was not to be. The musical taste of the world changed, and people embraced the new musical sensation which was "The twist" by Chubby checker.[2] Kerry Adams was soon forgotten and thus suffered a premature death at the hands of Chubby Checker. However, out of the ashes arose the man who gifted ophthalmology, one of its most loved invention, one which was a box office hit as far as ophthalmology was concerned and earned him the title "Ophthalmologist of the Century."

This is the fascinating story of Charles D Kelman who gave us phacoemulsification.

THE KELMAN CRYO STYLET

Charles D. Kelman, MD — Charlie [Figure 1] to all those who knew him was born on May 23, 1930 to Eva and David Kelman in Brooklyn New York. He graduated in medicine from the University of Geneva in Switzerland in 1956 and after that joined Wills Eye Hospital in Philadelphia for residency. It was during the residency that he achieved fleeting fame and glory as Kerry Adams. But when that ended suddenly, the disappointed Charlie turned his attention to Ophthalmology. He started his private practice as an Ophthalmologist in 1960. But Charlie as Kerry Adams had tasted something wonderful and exhilarating-the heady feeling brought in by fame, recognition, and audience applause. He now wanted the same from ophthalmology and began brainstorming with several ideas.[1] In July 1962, an article about Irving S Cooper and his cryoprobe use in brain Surgery appeared in the "Look" magazine, which he was subscribing to. He was hooked on to that. Dr. Kelman knew exactly how he wanted to use the cryoprobe in Ophthalmology. He needed to get into that lab and work on those ideas. Cooper who initially ignored the letters and phone calls from Dr. Kelman finally had to yield to the perseverance of the young ophthalmologist who showed up in his office uninvited and literally begged to be



Figure 1: Charles Kelman (Source: Wikipedia article on Charles Kelman. https://en.wikipedia.org/wiki/Charles_Kelman)

allowed the use of his lab couple of times a week. Working on cat's eyes the innovative Dr. Kelman soon found out that he could use the cryoprobe to extract out the lens easily and atraumatically. The jubilant innovator named his invention the " Kelman Cryo stylet." However, before he could take credit for the same, two other ophthalmologists already came out with publications on the method. Worse was to follow when Cooper, sensing potential of the cryoprobe, decided to expand on it and appointed a better-known doctor for the program at the expense of Charles Kelman.[2] Charlie was devastated. It was like Chubby Checker happening again.

THE IDEA

Dr. Kelman was not somebody who would accept defeat easily. He became more determined. The incident however made him paranoid about people trying to steal his research and probably resulted in him being too secretive about all his further research.[1] He decided to apply for a grant from the John A. Hartford Foundation for further studies in cryo, specifically on the effects of freezing on the ciliary body, retina, and the choroid. Having filled the application he went to bed unhappy and dissatisfied as he thought that the study aims were not enough to interest the foundation. In the middle of the night, Charlie woke up and almost as in a trance filled out some more lines, which changed his life as well as the ophthalmology landscape for ever. They were as follows. "In addition to the freezing studies, this investigator will develop a method for removing a cataract through an incision small enough so that no hospitalization will be required." It was the hardships of the elderly due to the extreme immobilization needed after cataract surgery which he had witnessed in the Will's eye hospital that probably led him to add those lines. He knew that the immobilization was necessitated by the giant incision needed to take out the lens, and the answer was to devise a method to take it out through a small incision. However, he did not have any idea how to do it. However, the chairman of the Hartford foundation thought otherwise, and a 3-year grant was approved.[3]

He convinced the authorities to give him some space in the research floor of the Manhattan Eye, Ear, and Throat hospital and set up his lab there. Charlie and his assistants moved into this space on the 10th floor of the building with cages of cats. Charlie was very secretive about the whole thing. Cheryll Jalbert, his favorite assistant, later remarked in an interview. "We were always conscious of somebody coming up the stairs, and the doors were always kept locked". For 2 years and 8 months, he toiled hard. He tried innumerable devices such as small drills, vibrators, manual disintegrators, rotating brushes, and small balloon-shaped bags for sucking in the lens to facilitate disintegration. He tried miniaturized meat cleavers and corkscrews. All that would happen was the lens spinning furiously damaging the corneal endothelium and iris. Nothing worked the way Charlie wanted. By 1966, both the funds and time allotted to him had been exhausted and Charlie had nothing to show for it other than hair which had grown to his shoulders, teeth which had developed scales and black circles under his eyes. He had been so obsessed with his research that he had neglected himself. It was time to stop, tidy up and report his progress to the foundation and try to get some more funds. Charlie had a haircut, and then he went to visit his dentist.

Dr. Larry Kuhn, the dentist used a newly acquired tool to remove the scales. It was the Cavitron dental cleaner which vibrated at ultrasonic frequencies flicking off the tartar of the teeth without damaging the teeth itself. The vibrating tip was being cooled by a stream of water. Dr. Kelman listened spellbound as the dentist explained its working to him. It was the Eureka moment for Kelman. He had the answer he was looking for. He became so excited that he ran out of the dentist's office shouting "I have got it! I have got it!" It was almost like Archimedes running shouting Eureka with one striking difference-clothes. While Archimedes did not have any, Dr. Kelman had in addition to his own, the dental bib around his neck too. The surprised dentist and his staff who did not have any idea what was it that he got or what had got into him was in for more surprise when Dr. Kelman returned an hour later with a freshly extracted cataractous lens in hand. He tried out the instrument on the lens and watched with delight as the vibrating ultrasonic tip engraved deep lines on the lens surface without the cataract itself jumping off from his hand. There it was! The Aha! moment. Charlie had found the answer he was looking for. He realized that he could use a suitably modified version of this instrument for disintegrating the cataract inside the anterior chamber without the lens spinning about.[2,3]

IDEA TO INVENTION

Without wasting any time, Charlie and his engineers with the help of Cavitron (later acquired by Alcon) designed a similar ultrasound probe [Figure 2] for the eye, but which incorporated both irrigation and aspiration rather than irrigation alone as in the dental probe.[4] It was working effectively in animal eyes, but still left the cornea opaque and white until he began using physiological saline imported from the Barraquer Institute. After several months of painstaking work and experimentation, in 1967, Charlie was ready for his first human subject, a man with a painful blind eye due to glaucoma already scheduled for enucleation. The patient

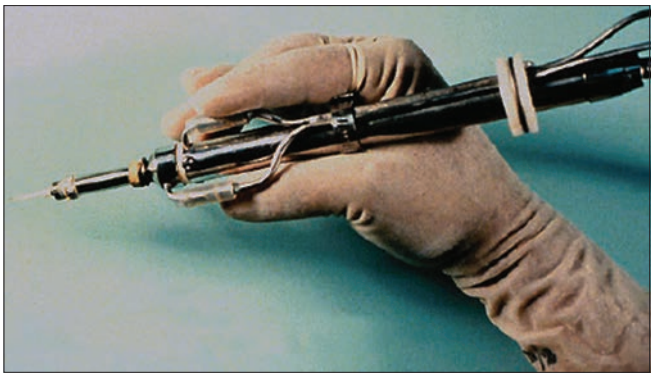


Figure 2: An early prototype of the phaco handpiece. (Source: https://crstodayeurope.com/articles/2018-novdec/phacoemulsification-in-2018/)

agreed to the experiment. The procedure was done in utmost secrecy. Charlie's paranoia had rubbed on to his assistants also. The large machine [Figure 3] was wheeled into the OT on the previous day by Charlie's favorite assistant and confidant Cheryl Jalbert who locked it in the nurse's locker room and slept there with the machine by her side. Dr. Kelman and his assistants started the surgery in the early morning to escape the attention of the head of the department of surgery, who was not very supportive.

The procedure took about 4 hours, and the phacoemulsification part alone took 70 min. The vibrating probe was quite heavy and Dr. Kelman struggled to control it. The disappointing experience in Kelman's own words was like this. "During the procedure, I found that the cornea was collapsing on to the probe. Happened about 30–40 times during the procedure. It could have ended there, because the next day, I had to remove the eye which was a bag of pus."[3]

However, one thing Dr. Kelman would never do was to give up on anything. He spent 2 years away, looking for a solution. Finally, he managed to find a company that had a device which could sense flow through an artery. This was incorporated into the aspiration line by Cavitron along with an air relieved valve. If the speed of the flow in the aspiration line exceeded that of the irrigation, the valve would open to immediately stop the suction.[4] This settled the issue to some extent. Furthermore, several improvements were made to the probe including increasing the tip vibrations from 20000 cycle/s to 40,000 cycles/s and decreasing the total weight. Almost a year later, after innumerable animal experiments, Charlie was ready to make one final attempt on another patient. This was a CRAO case with No PL vision. The surgery was a reasonable success. Although there was severe striate keratitis on the first postoperative day, it subsided by the 6th day. His results improved with the subsequent patients, and by the fourth patient, he was ready to announce his invention to the world. The Cryo episode had left an indelible mark on his mind.



Figure 3: Source: https://www.eurotimes.org/50-years-phaco/original-cavitron-kelman-phaco-machine

Dr. Kelman was not going to let anyone take away the credit of this dream invention. He patented his ideas and entered into a contractual agreement with Cavitron. He named the procedure Phacoemulsification. But Dr. Kelman and his procedure were set to have a tumultuous bumpy ride through an ocean of unprecedented resistance.

THE RIDE THROUGH TROUBLED WATERS

Charlie's methods were unconventional and unpalatable to many. Entering into a business relationship with an equipment manufacturer was considered scandalous at that time. There was staunch opposition from the chief surgeon of the hospital itself (Manhattan Eye and Ear Hospital) as a result of which the hospital appointed a committee to oversee the surgeries. To make matters worse Charlie did not do what was considered as accepted scientific practice of introducing new knowledge, which was publishing in peer-reviewed journals. Instead, with the help of Cavitron, he propagated his procedure by conducting meticulously organized weeklong training courses to selected practitioners. The news about the procedure and the course spread mostly by word of mouth. Charlie taught his students himself, painstakingly taking them through special tasks to improve hand-to-eye coordination and dexterity, familiarising them with the instrument as well with the operating microscope. His students were treated to a few of his shows also in the evenings, a mix of music and stand-up comedy. Charlie's actions irked the academicia and the major institutes. Phaco was described as malpractice and was declared experimental by even the National Eye Institute resulting in insurance companies declaring it nonreimbursable. In 1973, at the annual Welsh Cataract Symposium, the procedure was literally crucified by surgeon after surgeon sharing bad experiences and patients with poor results giving testimonials. As David Paton M. D,

would put it "the conference became the crucible in which phacoemulsification was thrust where upon it was left there to roast and boil."[2] In 1974 a committee constituted by the American Academy of Ophthalmology (AAO) concluded that Kelman's procedure did not have any additional benefits over Intracapsular Cataract Extraction (ICCE) and may not be suitable in many situations. The committee however accepted that the results were comparable to that of ICCE.

However, in the words of Charlie's wife Ann Kelman, instead of getting depressed as a normal person would have by this time, Charlie went in to the "It is not going to happen. I will show you" kind of mood.[2] He went to the public. He was a man of the stage and knew how to play to the audience. He organized a teaching course on Phaco at the Mt Sinai hospital and at the end had his not so receptive audience laughing by suddenly shifting to an entertaining musical show with his dancing girls suddenly making an appearance on the stage and dancing to his jazz rhythms. On February 21, 1975, Charlie shocked the ophthalmic community by appearing on the Tonight Show, Starring Johnny Carson, the most prestigious talk show on US television at that time. Dressed flamboyantly like a media personality Charlie joked with Carson on air chatted freely about phacoemulsification and even played his saxophone. He became sort of a celebrity overnight. His practice boomed, and he also became the darling of talk shows. However, phacoemulsification still remained in the back burner, practiced by Charlie and few of his good students. However, the advent of the foldable Intraocular lens (IOL) (Mazzocco taco) in the early 1980s changed all that. The tide slowly turned and Phaco began getting the acceptance it deserved. While watching his invention slowly becoming the norm in cataract surgery, his innovative mind was wandering over other horizons. He designed his own IOL and described the principles on which IOL design have to be based on. In the 1989 American Society of Cataract and Refractive Surgery (ASCRS) Binkhorst Lecture he touched upon some of his futuristic ideas, which included innovative use of electromagnets to break up the cataract in the eye, filling the empty capsular bag after cataract removal, with a clear gel made from the patient's own collagen thus restoring accommodation, etc.[1]

RECOGNITION FINALLY

It started with the Innovators award Lecture by the ASCRS in 1985 and he had his audience laughing with his opening statement- "I am deeply touched by this recognition which for most innovators is reserved for their funeral."[3] This lecture was subsequently (in 2003) named after Dr. Kelman himself.[5] Five years later in 1989, the society awarded its second prestigious award also to Dr. Kelman which was the Binkhorst Lecture. In 1999, Dr. Kelman was selected as one of the ten most influential ophthalmologists of the 20th century by the ASCRS and became president of the society.[6] The AAO after cold-shouldering Dr. Kelman for so long finally recognized his genius in 1991 when it gave a special recognition award to him and in November 2003 bestowed its highest honor, the laureate award on him.[1]

The country recognized him by giving him the National Medal of technology in 1992. In February 2004, he was inducted into the National Inventors Hall of Fame in Akron, Ohio. Posthumously he was awarded the Lasker award, the nation's highest honor for Medical Science.[6]

THE RESTLESS KELMAN

Charlie famously said during the Binkhorst Lecture "I have always been a Saxophone player wearing the mask of an ophthalmologist. If it was not for my parent's intervention, I would have carried on with my own dream, which is to be a musician." There were two sides to Dr. Kelman. The Innovator and the Show man. The two sides were sometimes competing for space and time and many a time complementing each other also. However, there was no doubt that, Dr. Kelman was at home most on the stage and that is why Ophthalmology has to thank Chubby Checker for kicking him off the stage at least for some time, time enough for his other side to take over and give us the fantastic gift of Phacoemulsification. However, even after fulfilling his father's dream, even after achieving success as an inventor, even after getting so many honours, Charlie's restless mind never felt fulfilled. To some extent, his love of performing music had been met by the performances he delivered at the end of his teaching courses in New York. But that was not enough. He took voice lessons and set up his own show at the Atlantis Casino in Atlantis City, New Jersey, where he performed regularly. He also performed on television as well as in the Carnegie Hall in New York, alongside several notable jazz musicians and entertainers. In 1985 He published an autobiographical masterpiece book "Through my Eyes." The book with the subtitle "The story of a surgeon who dared to take on the medical world." Is a must read for all physicians and young innovators.[1,3] He learned to fly and subsequently purchased a helicopter to commute from his office in Manhattan to his house on Long Island. He also took up golf, hiring a professional for several months to improve his technique as rapidly as possible.

EPILOGUE

Dr. Charles Kelman is fondly remembered as the father of Phacoemulsification. But in the words of his long-term

colleague Dr. Jack Doddick,[6] he is also the grandfather of small incision surgery in the entire human body as he was the first in any speciality to take out unwanted human tissue through a small incision. He passed away on June 1, 2004 after battling metastatic Lung Cancer for 6 years. As the technique that he gifted to the world reign supreme as the gold standard of Cataract Surgery, Dr. Kelman's own words (in his book "Through My Eyes") speak to us across the ages, sharing the secret of his success.

"I admit that I may have certain talents as an inventor, musician, and surgeon, but they are nothing compared to my ability to persevere, to keep going in the face of discouragement, to take the blows and stand up again."[3]

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EFFICACY AND SAFETY OF INTRAVITREAL AFLIBERCEPT TREAT-AND-EXTEND FOR MACULAR EDEMA IN CENTRAL RETINAL VEIN OCCLUSION: THE CENTERA STUDY

Jean-François K, Larsen M, Eter N, Bailey C, Wolf S, Schmelter T, *et al*. Efficacy and safety of intravitreal aflibercept treat-and-extend for macular edema in central retinal vein occlusion: The CENTERA study. Am J Ophthalmol 2021;227:106-15.

Retinal vein occlusion constitutes a large burden of retinal vascular disease globally. Macular edema and macular ischemia are the causes for reduction in vision in central retinal vein occlusion (CRVO), branch retinal vein occlusion as well as hemiretinal vein occlusion. CRVO could be ischemic as well as nonischemic. Although several treatment options existed conventionally including retinal laser photocoagulation, intravitreal corticosteroid injections and implants, and intravitreal anti-vascular endothelial growth factors (anti-VEGFs), there has been a paradigm shift toward the use of anti-VEGF agents consistently over the years.

The effectiveness of intravitreal anti-VEGF therapy is well established in the management of macular edema secondary to retinal vein occlusions. There is, however, a wide variation in the response to treatment among patients in terms of resolution of macular edema and improvement in best-corrected visual acuity. There may be good or early responders as well as partial or nonresponders.

The anti-VEGF agents could be administered using different dosing intervals. Most standard clinical trials in the field of anti-VEGF therapy used a fixed-dosing regimen, which is predictable and straightforward for both the treating doctor and the patient. The associated high, clinic and patient burden (especially with monthly visits), and risks of either over-or undertreatment, is a major issue with fixed-dosing intervals.

In *pro re nata* (PRN) regimens, patients are treated on disease reactivation in an effort to reduce injection frequency and costs. Patients typically follow a monthly schedule of clinic visits, where the decision to re-treat at each visit is based on a set of prespecified criteria, as determined by the treating doctor (e.g., visual acuity [VA] and optical coherence tomography/fluorescein angiography assessments). Outcomes obtained with this regimen depend largely on the re-treatment criteria employed and how closely these are adhered to. This is most commonly employed. Both these regimens do not factor in the patient response.

A treat-and-extend regimen is a more proactive and individualized approach to treatment, with the goal of preventing disease recurrence. This tailors the dosing interval based on patient response as well. The drug is administered at every scheduled visit, despite visual or anatomic status on the day. The interval between each visit is either increased or decreased according to the anatomic and VA status, to determine the maximum recurrence-free interval. The need for interim monitoring is minimized, which reduces the number of appointments per patient. *Post hoc* analyses of COPERNICUS and GALILEO supported the implementation of proactive treatment to prevent deterioration of functional and anatomic outcomes.

The aim of the CENTERA study was to assess the efficacy and safety of intravitreal aflibercept (IVT-AFL) administered in a treat-and-extend dosing regimen in patients with macular edema secondary to CRVO, as large-scale studies evaluating treat-and-extend regimens of IVT-AFL for the treatment of macular edema secondary to CRVO are lacking. Furthermore, even in studies demonstrating the benefit of IVT-AFL in the treatment of macular edema secondary to CRVO, the *post hoc* assessment of different dosing subgroups showed destabilization of disease with PRN dosing.

CENTERA was an open-label, multicentric, Phase 4 clinical trial of 162 patients, with center involving macular edema secondary to CRVO lasting <3 months. In this single-arm study, the patients received 2-mg IVT-AFL injections at baseline and every 4 weeks until disease stability criteria were met or until week 20, whichever occurred first. Starting at week 8, the re-treatment interval was adjusted by 2-weekly increments to maintain stable functional and anatomic outcomes.

The study found that 65.6% of patients gained ≥15 letters, from baseline to week 76. In the treat-and-extend phase, only 45.0% of patients achieved a mean treatment interval of ≥8 weeks. *Post hoc* analysis demonstrated that 63% and 68% of patients achieved a last and next planned treatment interval of ≥8 weeks, respectively, and a last actual treatment interval of ≥8 weeks was achieved by 63.1% of patients. The mean BCVA was 51.9 letters at baseline and 72.3 letters at week 76 (+20.3 letters). The mean central retinal thickness decreased from 759.9 μm at baseline to 265.4 μm at week 76 (−496.1 μm). These outcomes were comparable to other studies of IVT-AFL using fixed-dosing or PRN regimens.

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The *post hoc* analysis indicated that longer treatment intervals would have been achieved with longer study duration.

Ninety-three percent of patients in this study, however, had nonischemic CRVO. Although other studies such as the COPERNICUS and VIBRANT show the efficacy of IVT-AFL in ischemic CRVO as well, it remains to be studied whether the treat-and-extend dosing regimen would give similar results.

A high statistical power of ≥90%, inclusion of a broad range of baseline visual function (24-73 ETDRS letters), and early initiation of treatment were among the strengths of the study. Being a single-arm study with no active comparator, interpretation of the results is potentially limited. Furthermore, analysis of the last and next planned treatment intervals was *post hoc* in nature, which again limited the interpretation of the data. One hundred and thirty-one patients (80.9%) reported at least two treatment-emergent adverse events (TEAEs) during the study, and these TEAEs were predominantly mild or moderate in severity. The study does not discuss further regarding the benefit of a treat-and-extend regimen in terms of safety.

The authors concluded that clinically meaningful and significant improvements in functional and anatomic outcomes were achieved with IVT-AFL administered using a treat-and-extend regimen in patients with macular edema secondary to CRVO. The treatment intervals could also be extended beyond 8 weeks in many patients.

Studies exploring associated systemic risk factors such as diabetes mellitus and hypertension could further enhance our understanding regarding poor or nonresponse to treatment and help further modulate the treat-and-extend regimens. This would help reduce the financial burden on patients, especially in a setting like ours.

OUTCOMES OF GONIOSCOPY-ASSISTED TRANSLUMINAL TRABECULOTOMY IN PSEUDOEXFOLIATIVE GLAUCOMA: 24-MONTH FOLLOW-UP

Sharkawi E, Lindegger DJ, Artes PH, Lehmann-Clarke L, El Wardani M, Misteli M, *et al*. Outcomes of gonioscopy-assisted transluminal trabeculotomy in pseudoexfoliative glaucoma: 24-month follow-up. Br J Ophthalmol 2021;105:977-82.

Glaucoma is a progressive optic neuropathy that causes ganglion cell apoptosis and visual field loss, multifactorial in origin.

Pseudoexfoliation syndrome is an age-related systemic microfibrillopathy, characterized by progressive accumulation and gradual deposition of extracellular gray and white material over various tissues. It is one of the most common causes of secondary glaucoma and is associated with a worse prognosis than primary open-angle glaucoma showing reduced response to medications and faster progression, often requiring a surgical intervention.

Reduction of intraocular pressure (IOP) has been shown to slow glaucomatous progression, and IOP is the primary treatment target. Both glaucoma and its treatment can significantly affect the quality of life. Topical or oral IOP-lowering therapy, laser trabeculoplasty, and incisional glaucoma surgery (trabeculectomy and glaucoma drainage device implantation) formed the conventional treatment modalities.

The concept of minimally invasive glaucoma surgeries is revolutionizing the management of glaucoma. These techniques do not form a bleb, using an *ab interno* approach, and target the trabecular meshwork (TM), the primary anatomic structure responsible for aqueous outflow resistance.

Gonioscopy-assisted transluminal trabeculotomy (GATT) is a minimally invasive surgical technique in which a suture or catheter is used to bypass the TM circumferentially. The aqueous humor is thus shunted via the opened up TM, into the collector channels and flows out through the episcleral veins. The *ab interno* GATT procedure reports a remarkably good success rate, while negating several side effects of the earlier conventional scleral flap surgeries.

GATT being a relatively recent development in glaucoma management, the aim of this study is to present the outcomes of an *ab interno* GATT in eyes with pseudoexfoliation glaucoma (PXG) with a follow-up of up to 2 years.

This was a prospective, interventional, noncomparative case series and enrolled a total of 103 eyes from 84 patients with PXG. They showed progression of glaucoma despite maximal tolerated medical therapy. A 360°, *ab interno* trabeculotomy with gonioscopic assistance using either a 5.0 polypropylene suture or an illuminated microcatheter was performed. They were followed up to 24 months after surgery.

Main outcome measures were IOP, number of antiglaucoma medications, success rate (IOP reduction ≥20% from baseline or IOP between 6 and 21 mmHg, without further glaucoma surgery) and complication rate recorded at day 1, week 1, week 3, week 6, month 3, month 6, month 12, month 18 and month 24, or more frequently if clinically indicated by the physician.

Combined cataract surgery with GATT was performed in 50 eyes while the remaining 53 eyes were already pseudophakic. Postoperative IOP was significantly lower than baseline at all study time points for both groups. This reduction was statistically significant. The mean preoperative IOP was 27.1 (95% confidence interval [CI]: 25.5–28.7) mmHg using 2.9 (standard deviation: 1.1) glaucoma medications. An IOP reduction of 52% with a mean IOP of 14.1 (95% CI: 12.1–16.0) mmHg was achieved on postoperative day 1, with all glaucoma medications being stopped unless there was a postoperative IOP spike or steroid response.

The overall success rate was 89.2% at 24 months. Twenty-five cases had isolated IOP spikes, but there was only one case with transient hypertony. The overall complication rate was 2.9%. Low complication rate with a greater reduction of IOP and the cost-effectiveness of GATT, maintains the quality of life of the patient. The combination of cataract surgery and GATT maintained the same effectiveness as GATT alone in pseudophakic patients. There were six cases of partial trabeculotomy as well which were also successful.

The noncomparative design, the mid-term follow-up of up to 24 months, and the decreasing study pool due to some patients having the procedures performed <2 years before the end of this study were some of the limitations of this study. The adequacy of the sample size, therefore, is thus debatable. A switch from catheter-GATT to suture-GATT was made 1 year into the study due to economic reasons, and this limited the possibility of comparison between the groups. The success of the procedure depends on the anatomical integrity of the collector channels which cannot be assessed preoperatively, and this is a limitation of GATT. Furthermore, the number of patients having to be maintained on antiglaucoma medications postsurgery and the reasons for the same have not been discussed in detail. However, the requirement for antiglaucoma medications has definitely decreased at 24 months, which has been considered to be a factor pointing toward success of procedure.

The authors concluded that GATT safely and effectively lowers IOP in PXG and could even be considered as a suitable first-line treatment option given the relatively aggressive nature of PXG. The cost-effectiveness of the procedure can further be enhanced by using a polypropylene suture.

Early intervention using GATT achieves early control of IOP. Due to its *ab interno* nature, it leaves the option of a further conventional surgery like trabeculectomy with or without a drainage device later if IOP control fails in future.

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iTrace aberrometry - Identifying occult imperfections in the visual system

ABSTRACT

Visual acuity is the sum of qualitative and quantitative factors. A combination of both determines the final visual acuity. The quality of vision (QoV) can be easily assessed by documenting objectively the higher-order aberrations or by using subjective questionnaires available. The QoV is an integration of varied optical and neural factors. Similarly, the quantity of vision is documented by measuring uncorrected and best-corrected distance visual acuities. Optical aberrations are defect in a lens or a mirror prevents light rays from being focused at a single point and results in a distorted or blurred image. Moreover, they are the departure of the performance of an optical system from the predictions of paraxial optics. The QoV is primarily affected by both higher- and lower-order optical aberration. Aberrometers are the most vital instruments used for estimating optical aberrations so that a more comprehensive understanding of optical error can be quantified and corrected. A variety of aberrometers with different principles are available, such as Ray Tracing, Hartmann-Shack, Tscherning, and automatic retinoscopy. In this review, our prime focuses on Ray Tracing aberrometer, iTrace. This review will help all the ophthalmologists including residents and fellows learn the principle, features, and clinical applications of iTrace. The system integrates corneal topography with wavefront aberrometry, which has the unique feature of revealing the internal aberrations of the eye by subtracting the corneal aberrations from total aberration. It is the investigation of choice in the today's era considering patient satisfaction and visual outcomes, postpremium intraocular lens implantations.

Keywords: Corneal topography, iTrace, Ray Tracing aberrometer, wavefront aberrometry

INTRODUCTION

Human visual acuity is a sum of visual quality and quantity. Any deviation from these is qualified as poor visual acuity.[1] This can result from the poor quantity of vision which is calculated as uncorrected and best-corrected visual acuity. The quality of vision (QoV) is documented objectively by calculating the higher-order aberrations (HOAs) or by using subjective questionnaires available.[2] Visual acuity is primarily determined by tear film dynamics, cornea aberrations, pupil size, lenticular aberration, and retinal pathology.[3] The first three are the major causes of optical aberrations. Optical aberrations are one of the major causes of poor QoV. Optical aberrations are synonymous with refractive errors. Most of us are familiar with myopia, hyperopia, and astigmatism, which are labeled as a lower-order aberration (LOA).[4] In routine practice, optometrists have been correcting LOAs for over a century with spectacles. However, what about HOAs such as coma, trefoil, and secondary astigmatism. They cannot be corrected by spectacles and are a major source of patient dissatisfaction considering the QoV.[5] The aberrometers are intended to measure the deviation of rays at the retinal plane of focus when the light rays pass through the pupil.[6] There are a variety of aberrometers available in the market in the form of Hartmann-Shack, Tscherning, Ray Tracing, and automated aberrometers. They help in diagnosis and

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treatment of various optical pathologies in the eye.[7] iTrace is a Ray Tracing aberrometer that employs both wavefront (WF) aberrometry and Placido corneal topography (CT). It can calculate corneal, lens, and total aberration separately along with topographic screening.[8] Recently, it has gained immense popularity for preoperative and postoperative evaluation and management of cataract and refractive surgery patients.[8]

BEFORE UNDERSTANDING ITRACE AS A WHOLE, WE MUST UNDERSTAND FEW IMPORTANT TERMINOLOGIES

Wavefront

It is a line drawn perpendicular to all rays of light entering/exiting the eye. The WF is flat or plane WF until it hits the curved surface of the eye. The more distorted the optical system, the more distorted the WF. The parallel beams have a parallel WF, while the converging beams result in a spherical WF.[9]

Aberrations

They are imperfections in the image formation of the optical system. In other words, they are also defined as a defect in the lens or the focusing mirror that prevents light rays from being focused at a single point and results in a distorted or blurred image. They are also defined as the difference in optical path length between any ray passing through the pupillary plane and the chief ray passing through the pupillary center.[10]

TYPES OF ABERRATIONS

Diffraction

Bending of light rays caused by the edge of an aperture of the rim of a lens. The actual pattern of the diffracted image produces a circular aperture or pupil is a series of concentric bright and dark rings.

Chromatic aberration

Chromatic aberration, also called "color fringing" or "purple fringing," is a common optical aberration that occurs when a lens is either unable to focus all wavelengths of color to the same focal plane and/or when wavelengths of different colors are focused at different positions in the focal plane. It is a result of lens dispersion, with different colors of light traveling at different speeds while passing through a lens. As a result, the image usually looks blurred, or noticeable colored edges (red, green, blue, yellow, purple, and magenta) can appear around objects, especially in high-contrast situations.

Spherical aberration

It is an optical problem that occurs when all parallel rays of light focus at different points after passing through a spherical surface. The ray of light passing through closer to the edge or "periphery" of the lens is refracted more than near its horizontal axis. Hence, they end up in different spots across the optical axis. These aberrations affect the resolution and clarity, making it difficult to obtain sharp images.

Geometric aberration

They are caused by the change in the geometry, i.e., shape of the lens and mirror. They are also called monochromatic aberrations because they occur for images formed with the light of a single frequency. Common examples include coma, distortion, decentering, astigmatism, and field curvature.

Oblique aberration

Objects in the peripheral field are seen by the oblique incident narrow pencil of rays, which are limited by the pupil. Thus, refracted pencil show oblique astigmatism.[11]

CLASSIFICATION

1. LOAs - Myopia, hyperopia, and regular astigmatism
2. HOAs - Spherical aberrations, coma, decentering, chromatic aberrations, oblique astigmatism, and centering.[4]

WAVEFRONT ABERROMETRY

WF aberrometry is an objective method of measuring the refractive power of the eye. The aberrometers give detailed measurements and interpretation of the movement of the light WF. When parallel rays of light pass through the pupil and are reflected by the retina, the WF of the reflected beam is recorded and compared to that of the reference WF. All the points of variation are recorded and measured, creating in turn an optical fingerprint. It assists in the diagnosis of both higher-order and lower-order refractive errors.[12]

DIFFERENT TYPES OF ABERROMETER

Types of WF testing:[13]

1. Ingoing WF aberrometry - Retinal image aberrometry
2. Outgoing WF aberrometry - Hartmann-Shack sensor - e.g., Zywave
3. Double-pass aberrometry - Automated slit skiascopy
4. Ingoing subjective adjustable aberrometry - Spatially resolved refractometry
5. Tscherning's aberrometer - Tracey retinal ray tracing - e.g., NIDEK OPD Scan

RAY TRACING – ITRACE

Concept of Ray Tracing

In this method, the parallel laser beam passes across the line

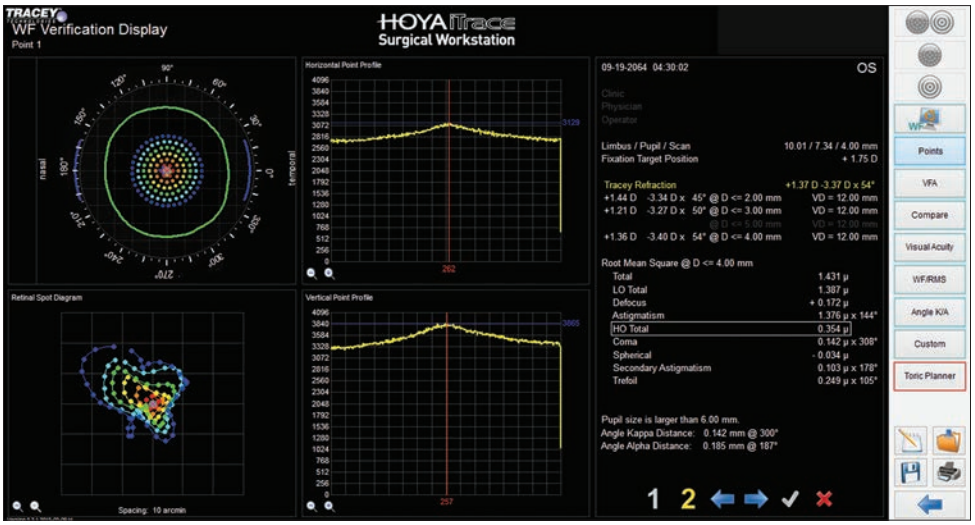


Figure 1: Image of the iTrace depicting the wavefront verification display along with retinal spot diagram pattern. The vertical point profile is slightly higher than the horizontal point profile, but the pattern is uniform

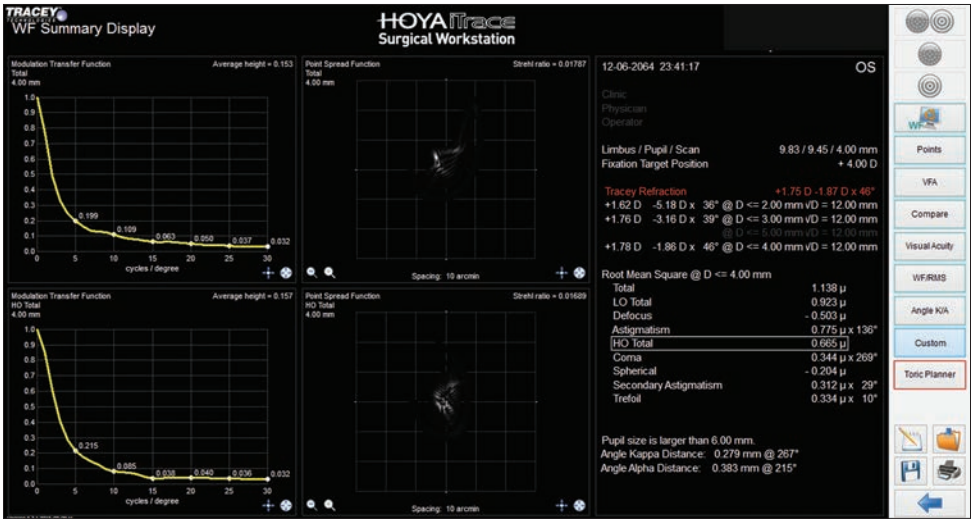


Figure 2: Image of the iTrace depicting defocus suggestive of refractive error

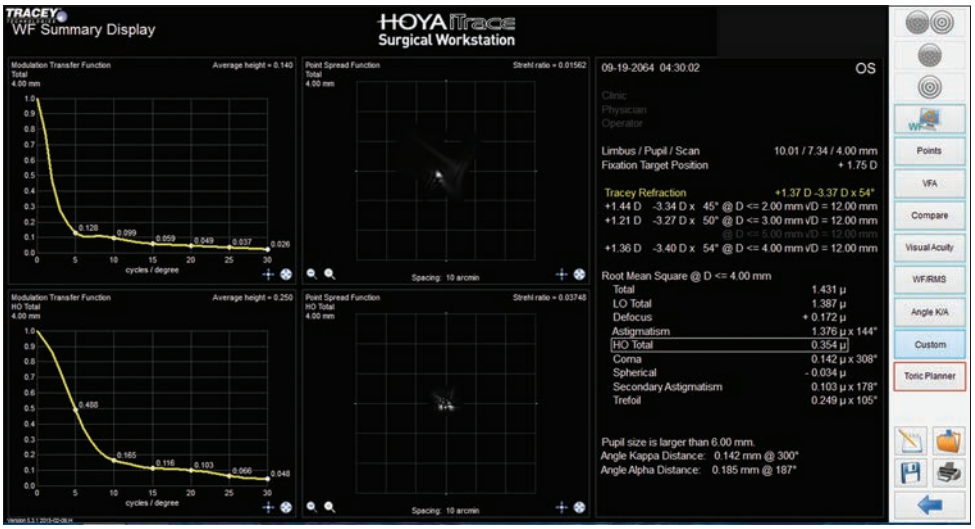


Figure 3: Image of the iTrace depicting modulation transfer function of a patient with refractive error. Note the slope will be uniform in an emmetropic patient

of sight through the pupil. The aberrometer employs the retroreflected light captured by reference linear sensors to measure the exact location where the laser beam strikes the retina. The local aberrations that are present in the path of the laser beam and that pass through the cornea and internal structures cause a shift in the location of the retina. Thus, laser beam is shifted to another point, and thus, multiple points are projected onto the retina. These laser beams pass through multiple points on the pupil. By this process of entrance and exit of laser beams, a real WF error is obtained. This method helps obtain the forward aberrations of light that go through the pupil.[14]

UNDERSTANDING RETINAL SPOT DIAGRAM, POINT SPREAD FUNCTION, AND MODULATION TRANSFER FUNCTION

Retinal spot diagram

When several laser points pass through the pupil and are projected on the retina, a retinal spot diagram (RSD) is created. The RSD reveals the patient's refractive error, aberration, and data of point spread function (PSF) [Figure 1].[15]

Point spread function

It simply means the spread of points on the retina once the spots are projected through the pupil. The morphological pattern obtained gives an idea of the degree of WF qualitative aberrations. The smaller and sharper the PSD, the better the resolution [Figure 2].[15]

Modulation transfer function

It describes how details of the objects are obtained in the form of the image produced by the lens. In other words, the modulation transfer function (MTF) and PSF define the optical system's ability [Figure 3].[15]

PRINCIPLE OF ITRACE

iTrace employs the basic principle of ray tracing as described above. Here, series of infrared beams (100 μm) of 785 nm wavelength pass parallel through the pupil in the line of sight and project on the retina. Once this position has been obtained, the laser beam is shifted sequentially to another point on the retina. In this way, 64 laser beams are projected through the entrance pupil 4 times each (256 points) at a rapid speed of 250 ms. In this way, a pattern is obtained RSD (map) of all the projected points, and a WF is reconstructed revealing the occult aberrations. In an emmetropic system, normally, all the points will concentrate over a single focus macula. Any local aberrations when the beam enters the cornea or the lens cause a shift in the location of the retina, concerning the reference focus points. The major advantage of iTrace over other aberrometers is that other rectilinear or polar patterns can also be obtained. The iTrace uses concentric rings to depict the pattern.[15]

COMPONENTS

The panel and the components of iTrace are collectively labeled as the data acquisition unit. Through this, the laser beams are projected onto the retina and then processed through the inbuilt software. The unit has an inbuilt optometer, pupil size detector, and adjustable focus. The optometer helps by aligning the patient pupillary axis to the laser beam projection axis and simultaneously helps by relaxing the accommodation of the patient by using the principle of fogging (+7D to −5D). In addition, it has a corneal topographer to map the cornea [Figure 4].

TECHNICAL PREREQUISITES TO BE FULFILLED TO GET A CORRECT GRAPH

Specifications of the i-Trace system: [16]

1. Refractive power range: ±15 D sphere, ±10 D cylinder
2. Pupil diameter: 2.5–8 mm
3. Accuracy: ±0.10 D
4. Reproducibility: ±0.10 D
5. Topographic cone 24 rings
6. Measured and analyzed points: 8640
7. Corneal coverage: 8 mm on 42.5D sphere
8. Dioptric range: 33.75–61.36D
9. Capture mode: auto and manual
10. Dimensions: 13 inch (33 cm) ×17 inch (43.2 cm)
11. Weight: 27.4 lb (20 kg).

INTERPRETATION OF RESULTS

Itrace provides measurements in the form of few basic maps. These maps are described below[17]



Figure 4: Image of the iTrace depicting the data acquisition unit of iTrace measurement system which combined the features of wavefront aberration along with Placido-based topography

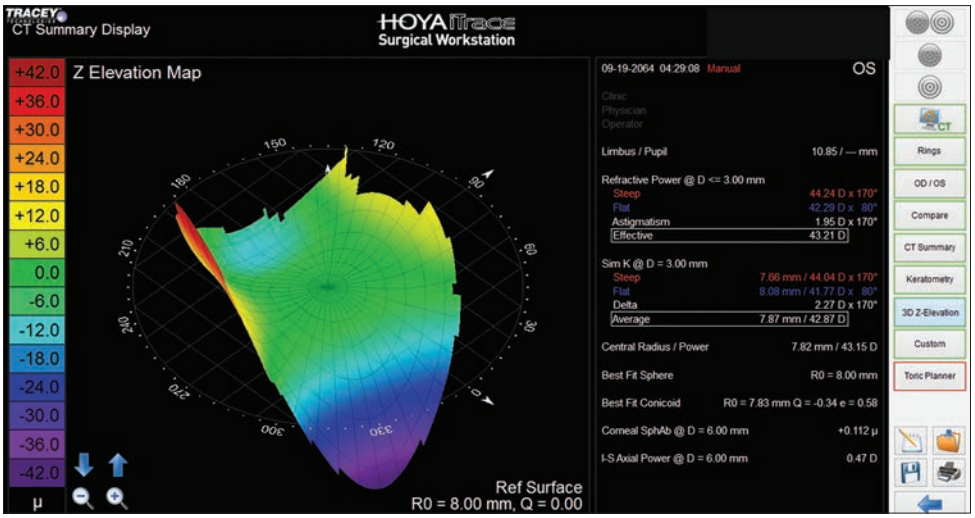


Figure 5: Image of the iTrace depicting the corneal topography summary display showing Z elevation map

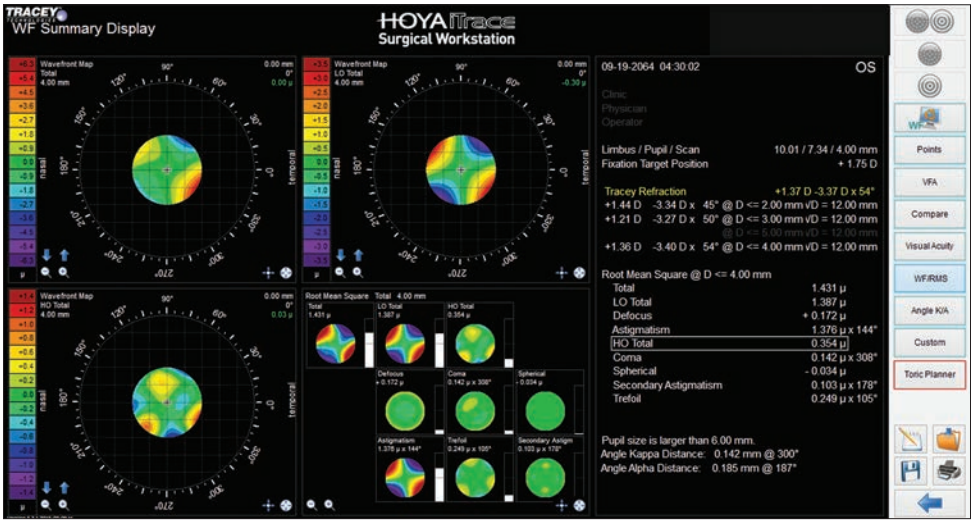


Figure 6: Image of the iTrace depicting the wavefront verification display with root mean square map of all the aberration of the patient

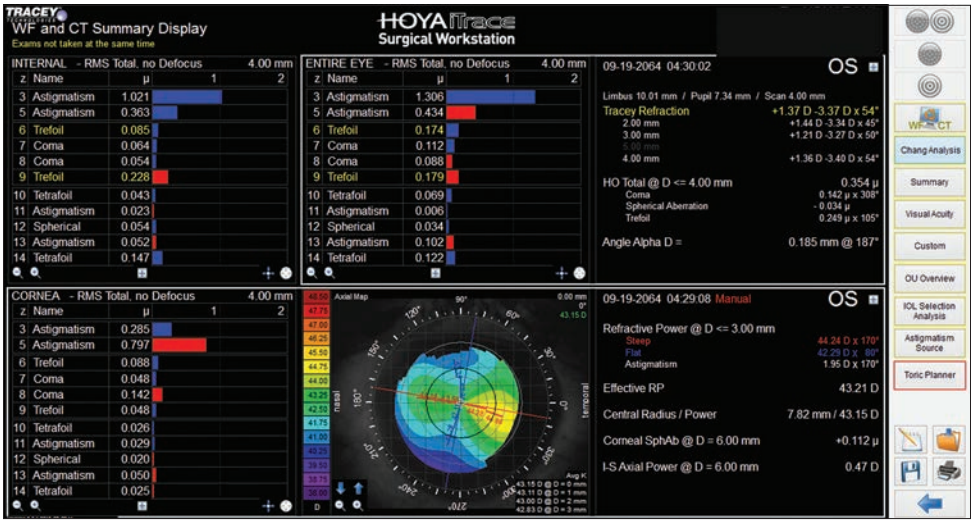


Figure 7: Image of the iTrace depicting the total and higher-order aberrations of the patient

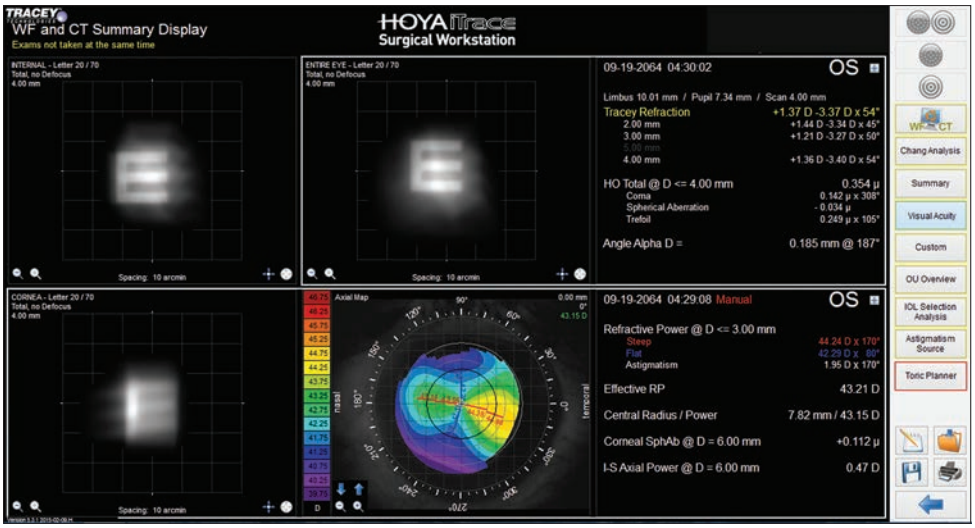


Figure 8: Image of the iTrace depicting blurred image of Snellen E with an acuity of 20/70. The blurred vision is a combination of corneal and lenticular aberrations

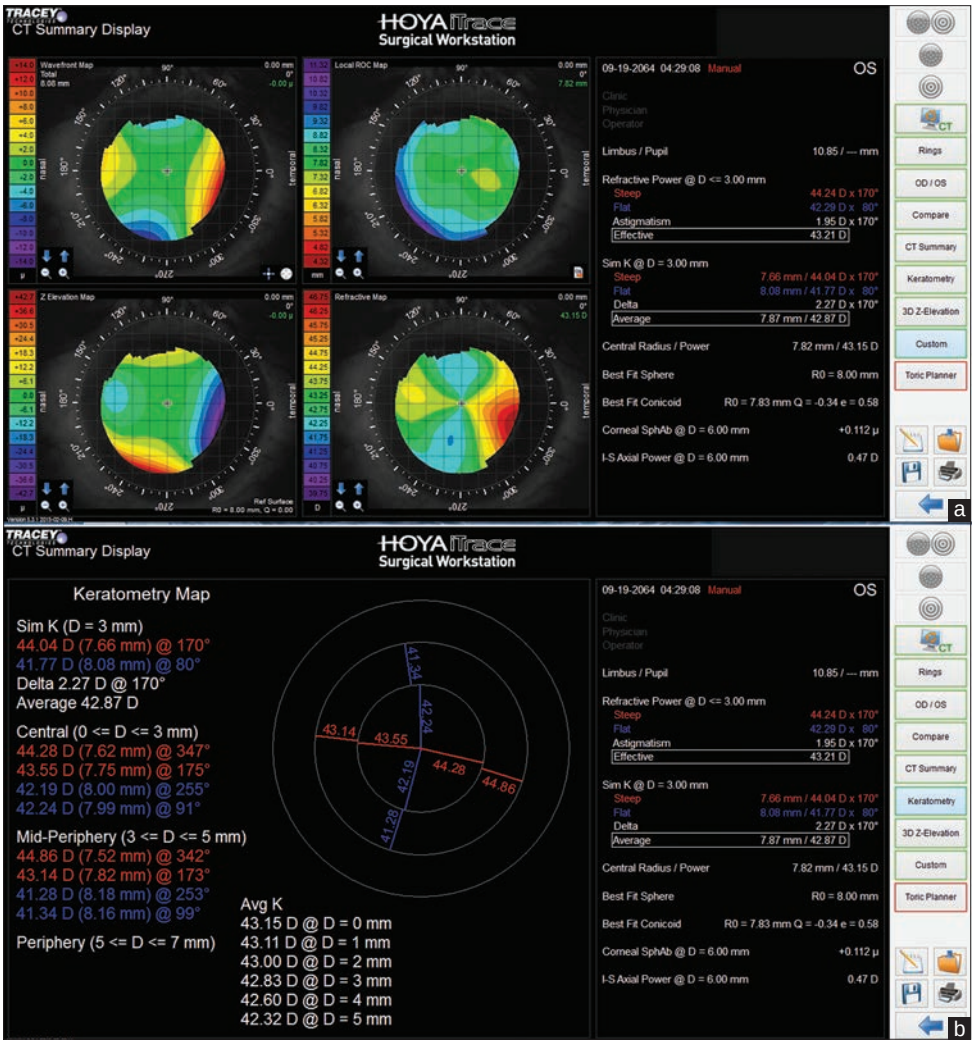


Figure 9: (a) Image of the iTrace depicting corneal topography summary display showing the wavefront map, Z elevation map, local ROC map, and refractive map. (b) Image of the iTrace depicting the keratometry map

Wavefront map (total and higher-order aberration)

This map reveals the WF aberration which is color coded and values are measured in microns. The total map gives both HOA and LOA, and HOA reveals higher aberrations such as coma, trefoil, and spherical aberration. Warm colors indicate that the WF aberrations are in front of the reference plane while cooler colors indicate that the WF aberrations are at the back of the reference plane. For example, red indicates warmer, green indicates neutral, and blue indicates cooler colors [Figure 5].

Root mean square

The root mean square (RMS) is the quantitative analysis of the magnitude of the aberration. This gives a total RMS value for the total ocular aberration of the eye and a specific RMS value for each Zernike term or component of the eye. The measurements are taken in microns and up to sixth-order aberration can be assessed [Figure 6].

Total refractive and higher-order aberration refractive map

In this map, the refractive power of the eye is depicted in diopters. Myopia is denoted by red, emmetropia in green, and hypermetropia in blue. The measurement taken is for the whole eye rather than corneal power alone. The combination of the refractive and the topographic map display gives an idea of whether the astigmatism is corneal or lenticular. In addition, accommodation can also be measured by obtaining the maps at various distances and assessing the refractive change [Figure 7].

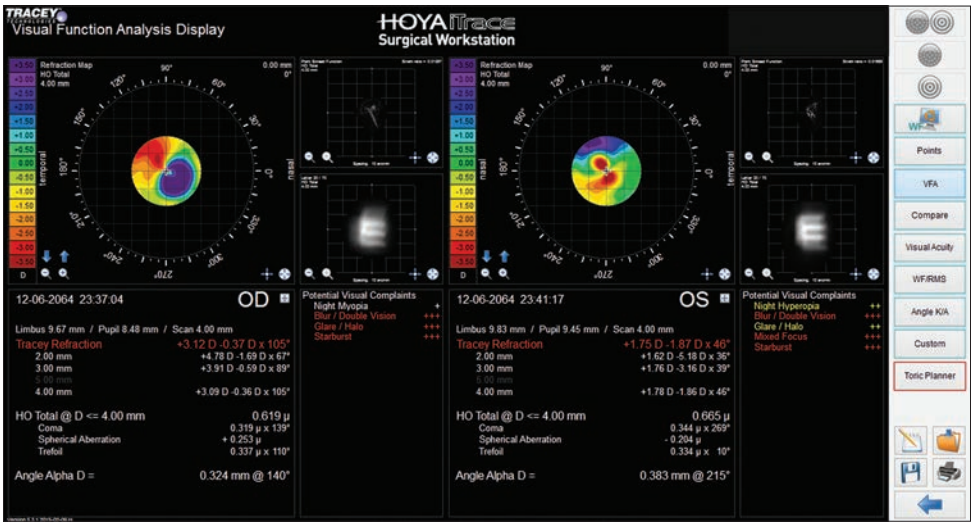


Figure 10: Image of the iTrace depicting the visual function analysis display comparison of the two eyes showing the potential visual complaints such as glare, halo, and starburst

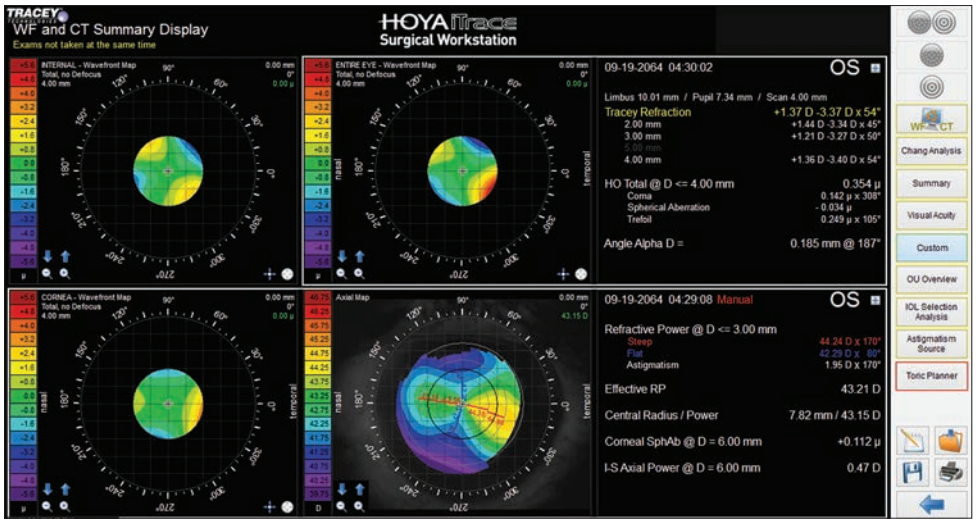


Figure 11: Image of the iTrace depicting combined wavefront and corneal topography summary display

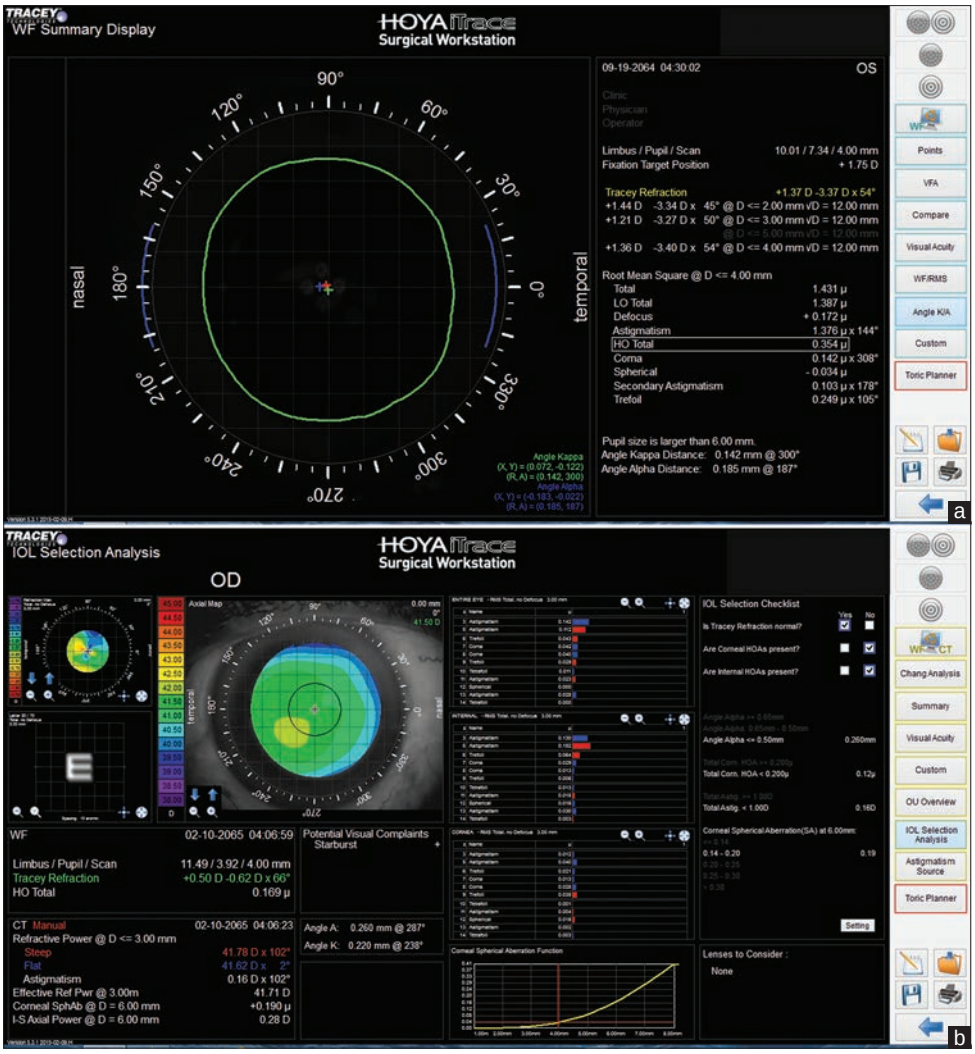


Figure 12: (a) Image of the iTrace depicting the angle kappa for premium intraocular lens analysis. (b) Image of the iTrace depicting the intraocular lens selection analysis based on various aberrations

Point spread function - Total and higher-order aberration

It represents the quality and sharpness of the image obtained in the optical system. When point source of light passes through the pupil and strikes the retina, the morphological pattern is obtained is the PSF. The higher the aberrations and refractive error, the greater is the defocus. An emmetropic eye gives a well-centered focus [Figure 2].

Snellen letter - Total and higher-order aberration

This map is a measure of how the human eye will see the letter "E" at various grades of visual acuity 6/6, 6/12, 6/24, 6/36, and 6/60. This helps the ophthalmologists or optometrists to assess how are the patient's QoV and any discomfort reported by the patient [Figure 8].

Modulation transfer function

This helps obtain images produced by the optical system in terms of details of the object. This function is a measure of contrast sensitivity and resolution of an image at various spatial frequencies [Figure 3].

Zernike polynomials

This map displays the Zernike polynomials (ZPs) giving a detailed analysis of specific aberrations in the eye. The iTrace only displays ZP up to sixth order with 27 terms, with total internal aberrations, corneal, as well as the difference between the cornea and total of the eye.

Aberration of internal optics

This map and property are unique to the iTrace system which provides important information combining WF analysis (WFA) with CT. CT maps mathematically generate the corneal aberration. These aberrations when subtracted from the total aberrations give the internal aberrations of the optical system. This features to distinguish and separate the corneal and internal optical aberrations.

CORNEAL TOPOGRAPHY

The iTrace has an inbuilt Placido (Vista) topographic system (Eyesys Vision Inc., Houston, TX, USA) to assess the corneal aberrations. The system covers the central 0.6 mm and up to 10 mm of the peripheral cornea.

The topography system helps to analyze:

1. K reading (3 mm zone)
2. Refractive corneal power (3 mm zone)
3. Corneal indices - Inferior-superior asymmetry, potential corneal acuity, aspheric factor-quality index (Q), uniformity index, and spherical aberrations of cornea
4. Topographic map display - Axial map, tangential map, elevation map, refractive map, and WF map [Figure 9a and b].

DATA ANALYSIS

1. WFA - There are two displays.
   a. Visual function analysis (summary display) shows the total HOA either the refraction map or the WF map. This display gives a detailed insight into refraction (various diameters), RMS, PSF, Snellen letters, and symptoms such as myopia, glare, and halos. The symptoms are graded 1–3 depending on the intensity, and the pupil diameter can also be altered with the help of the regulator at the bottom [Figure 10]
   b. WF comparison map gives the display of two maps in a single patient. First, the refractive map for comparing aberration preoperatively and postoperatively, and second, the accommodation map.
2. Corneal topogrpahic analysis (CT summary display) has been discussed in the respective section

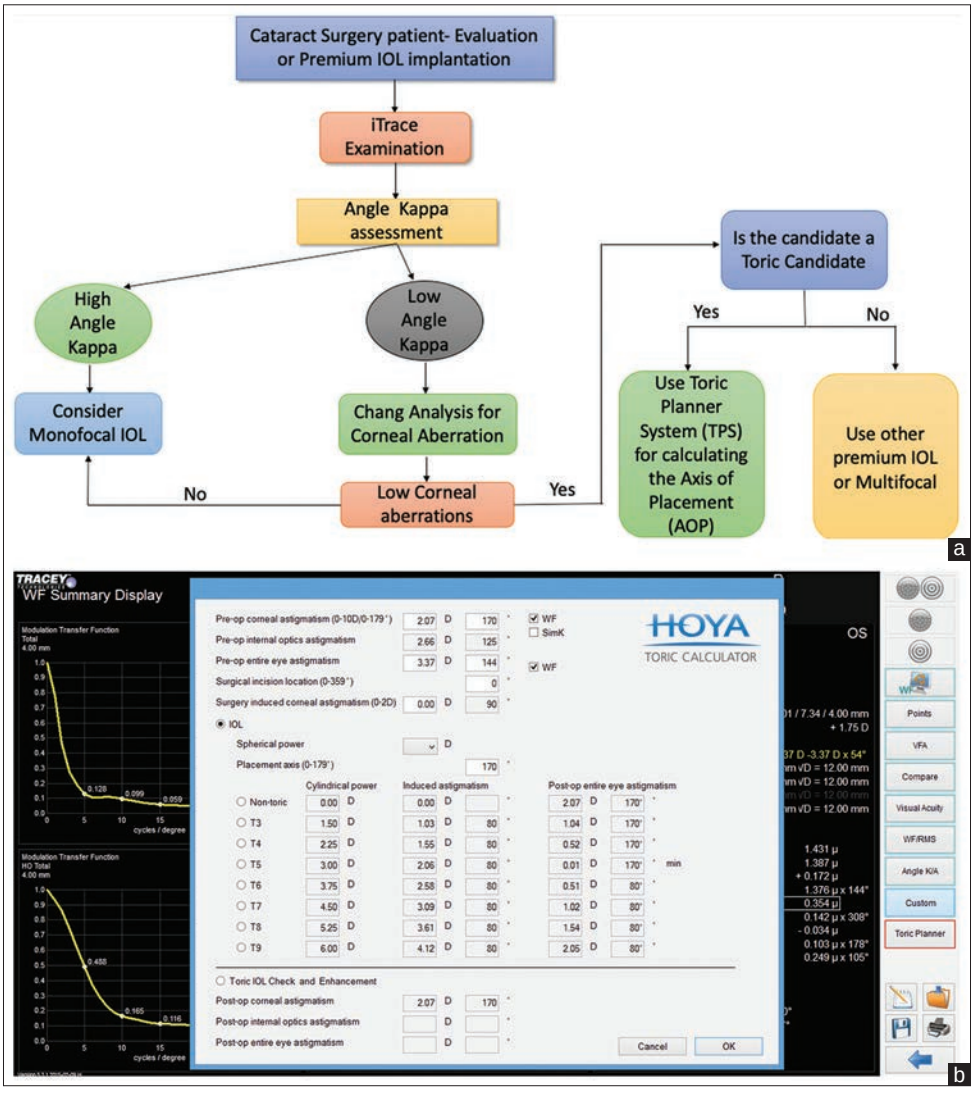


Figure 13: (a) Flowchart for premium intraocular lens selection. (b) Image of iTrace depicting the inbuilt toric planning system having the toric calculator for intraocular lens power and axis placement

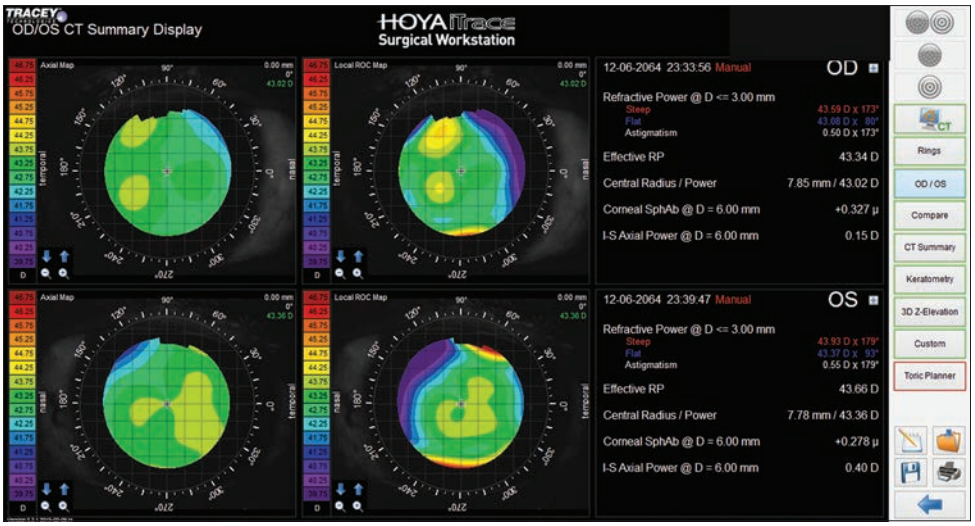


Figure 14: Image of iTrace depicting the comparison of both eyes corneal topography summary display

3. Combined WF and topographic (CT) analysis (summary display) [Figure 11].

CLINICAL APPLICATION

1. Aberration - WF verification with the help of RSD and RMS WF values allows rapid diagnosis of LOAs and HOAs
2. Visual function, quality, and symptoms - The iTrace gives the summary of multizone refraction analysis, PSF analysis, Snellen E simulation analysis, and potential visual complaints
3. The iTrace has the unique feature to separate corneal and lenticular aberrations
4. CT monitors the corneal changes between examinations and identifies the absolute effect of contact lenses, refractive surgery, and corneal warpage
5. Accommodation - Identify changes in accommodation up to 4D
6. Visual acuity analysis - Preoperative and postoperative total visual acuity changes after cataract and refractive surgery, contact lenses fitting, or spectacles usage
7. Keratoconus screening - Using CT maps and by employing Rabinowitz criteria [Figure 9a and b]
8. Contrast sensitivity helps in the assessment of CS based on MTF, RMS, and PSF
9. Choosing premium intraocular lens (IOLs) such as multifocal and toric IOL based on an assessment of angle Kappa. A high angle Kappa is a contraindication for implantation of premium IOLs [Figures 12a, b and 13a, b]
10. It also helps in postoperative of IOL in the form of IOL tilt and centration
11. The early cataract changes are reflected by the lens aberrations
12. The internal aberrations can also result from the posterior capsular. Opacification can be reconfirmed by slit-lamp examination
13. It can also display characteristics of both eyes simultaneously for comparison [Figure 14]. The other uses include corneal inlay planning, dry eye management, vitreolysis, and dysfunctional lens syndrome.[15-17]

FUTURE DIRECTION

iTrace besides being a diagnostic and therapeutic tool has a big future, considering research globally. It will also serve as an educational tool for patients, ophthalmologists, and trainees with a variety of inbuilt technical features.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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Prevalence and risk factors for refractive errors in Kerala

Dear Sir,

I wish to bring to your attention the high prevalence of refractive errors in the state of Kerala in South India. Refractive errors in schoolchildren are a common and treatable public health concern that has long-term implication of the vision and overall development of children. Several studies from 4 districts of Kerala have reported a prevalence of refractive errors that range from 15% to 30% and suboptimal use of spectacles.[1-7] The reported prevalence is much higher than 7.5% prevalence of refractive errors reported by Agarwal *et al*.[8] in their meta-analysis of 59 quality assessed studies from India. The significantly higher prevalence of refractive errors in schoolchildren of Kerala is a matter of grave concern. The fact that no studies from Kerala were included in the meta-analysis is also a matter of grave concern.

It is possible that the higher prevalence of refractive errors, especially myopia that is the most common refractive error, is associated with environmental risks. The association of myopia with increased near work at early ages, higher educational level of children and parents, higher socioeconomic status, and intelligence is recognized. Kerala is a highly literate state with an almost 100% school participation rate among children. There is also an increased use of digital devices for learning and recreation, working on computers, playing video games, and watching content in handheld devices. Smartphones are affordable and easily available and used often for work and leisure. The possible association with environmental factors is supported by a previous study that reported an urban-rural difference in the prevalence of refractive errors.[9]

The importance of refractive errors is acknowledged by the Kerala Society of Ophthalmic Surgeons (KSOS) association that has started Baladarshan, a program to sensitize the schools regarding refractive errors and improve the early detection of refractive errors in children. However, we feel more must be done. The high school participation rate provides us with the opportunity to obtain reliable data on refractive errors from all districts and to provide appropriate services. More high-quality studies must be conducted preferably using standardized methods to ascertain age-specific prevalence, incidence, and risk factors and to plan for appropriate service delivery. High-quality research is essential to find the annual proportion of newly detected refractive errors and the dropout rates for the use of spectacles or contact lenses. Newer interventions for the management of high myopia and refractive errors are available and must be evaluated. The centrally sponsored school vision screening program of NPCB must integrate with the state's Sarva Shiksha Abhiyan program, and there must be mandatory regular school-based vision screening of all children using age-appropriate visual acuity tests. It is also necessary to complement visual acuity testing with assessments of functional vision in children particularly in children with development and neurocognitive delays. The high prevalence of refractive errors is a challenge that must be addressed to preserve the long-term ocular health of our future generations. The association of KSOS is uniquely placed and must play a leadership role to develop clinical and research and service delivery protocols and guidelines to address refractive errors of schoolchildren in Kerala.

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Conflicts of interest

There are no conflicts of interest.

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Prevalence and risk factors for primary glaucoma in Kerala – The need for information

Dear Sir,

We wish to highlight the lack of population or hospital-based information on the prevalence and risk factors for glaucoma from Kerala. Glaucoma is reported in an estimated 11.2 million persons aged 40 years or older in India.[1] Primary open-angle glaucoma (POAG) is more common with an estimated 6.48 million persons and primary angle-closure glaucoma (PACG) is reported in an estimated 2.54 million persons.[1] An estimated 27.6 million persons may have any form of primary angle-closure disease.[1] Population-based studies from South India have reported varying prevalence rates for glaucoma that vary from 0.4% to 4% for POAG and 0.5% for angle-closure glaucoma with a reported urban rural difference in the prevalence.[2-6] Increasing age and increased intraocular pressures are reported as risk factors for POAG, and increased age, female gender, short axial length, thicker cornea with steep corneal curvature, and thicker lens with anterior lens position were found to be significant risk factors for PACG.[2,7,8]

Glaucoma can lead to irreversible blindness and an estimated 1.5 million people are blind from glaucoma in India. It is estimated that over 75% of the people with glaucoma are undiagnosed in low- and middle-income countries including India.[9] Knowledge of the estimates of the magnitude, risk factors, consequences of glaucoma, and prevalence of undiagnosed glaucoma are important to develop appropriate screening and diagnostic strategies. Population-based estimates from the other South Indian states may be considered as a surrogate for the magnitude of glaucoma in Kerala but may be unreliable when we consider the large variation in the prevalence measures among those studies. In addition, all the major prevalence studies on glaucoma from Southern India are more than a decade old and we cannot be sure if those estimates are applicable now. Glaucoma is a disease that is more common in the elderly and the prevalence or proportion of glaucoma may have increased as the population demographics have changed toward aging in Kerala.

It is important that Kerala has a state-level strategy to address this important cause of irreversible blindness. These must include standardized strategies for screening, diagnosis, and strategies to improve the reach and outcomes of therapeutic interventions. Accurate baseline estimates of the prevalence and incidence, risk factors, and prognostic factors for glaucoma are essential to understand the effectiveness of interventions at a population level.

The Kerala Society of Ophthalmic Surgeons must consider the feasibility of multicentric studies across several regions and diverse health care settings of Kerala to address the lack of information on glaucoma from Kerala.

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Conflicts of interest

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Has COVID-19 changed long-term clinical practice – The new abnormal?

Dear Sir,

On March 11, 2020, the World Health Organization declared COVID-19 officially as a pandemic after casking through 114 countries in 3 months and infecting over 118,000 people with an incessant spread ever since.[1] Pandemics have large-scale outbreaks of infectious disease with a high morbidity and mortality load across the globe and cause significant economic, social, and political disruption. COVID-19 is caused by a new strain that was not previously found in humans. It has been straining health systems worldwide and is expected to cause an economic recession matchless in a recent history.[2]

In the causatum of COVID-19, there will be significant lined up demand for health-care services. This pandemic has put the notoriety on digital health tools such as telehealth and remote monitoring as health-care professionals had to swivel to technology to take care of patients quickly. Thereby making digital health from a "nice to have" to a must-have. Even in remote places of a geographically diverse country, the increased use of technology and opening up telemedicine will improve access to health care. Innovations of at-home diagnostic equipment will enhance the ability of professionals to do remote virtual care. In addition to virtual checkups, hospitals and clinics will stick COVID-era operations, visitor, and design protocols together long, well after the pandemic.

As emergent takes pre-eminence over critical, the entire system is likely to miss opportunities for timely diagnosis and treatment of other diseases due to the focus on prevention, diagnosis, treatment, and containment of the pandemic. Patients with chronic disease, keeping on one's toes of going out, or facing difficulties in migrating due to lockdown restriction might end up with long-term sequelae because of missing on treatment. These will raise the overall burden of diseases in a region to a certain extent by eventually raising the possibility of complications and worsening the disease.

Health systems will recognize and consider that patients may not want to get surgery in a hospital; they will need to be reassured that it is safe to enter hospitals and other health-care facilities. For those who have put off elective surgeries and procedures, some organizations with ambulatory surgery centers will start providing patients with the option to have their surgery in such places.

Another significant impact of the COVID-19 pandemic has been on how patients work and live with social distancing measures. With that in mind, there will be advancements in drones and robotics in the consumer world including delivering medicines to reduce the number of people who interact with other people.

Public current concerns with personal hygiene maintenance, using mainly nose/mouth protection, anti-infections material for environment and clothing, and hand sanitizers, will go a long way. This consumption may remain in behavioral reflexes of the public, globally, and locally, with the pandemic's extended period.

Thus, as we face this prodigious confrontation and focus consummating through with minimum gnaw to human lives, health-care scenario, and clinical practice have to go a long way to unravel ulterior opportunities. Has COVID-19 changed long-term clinical practice? Yes absolutely, and by identifying these changes and impacts, may guide health-care professionals in evidence-informed devising and decision-making to tackle associated challenges.

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Comment on "the champion runner who became the forerunner in ophthalmic surgery training"

Dear Sir,

I happened to read the very informative article by John C B, titled "The champion runner who became the forerunner in ophthalmic surgery training," published in the Kerala Journal Of Ophthalmology,[1] and I would like to congratulate the author for highlighting another aspect of the great surgeon Dr. H. B Stallard. In this context, I would like to narrate a true incident that happened in 1959, which was described to me by my Grandfather, Dr. P. B. Menon, L. O, the first qualified Ophthalmologist of Kozhikode, Kerala, and the Malabar region.

Sri K. P. Kesava Menon was one of the Founders of Mathrubhumi Printing and Publishing Company and was also its Managing Editor. He was a high myope. My Grandfather, Dr. P. B. Menon was his close friend and also his Eye Specialist. In 1959, Sri. KPK Menon developed bilateral cataract, and he approached my grandfather for deteriorating vision. Dr. Menon, after a thorough examination with Torch and Direct ophthalmoscope, was of the opinion that there was a retinal detachment affecting one quadrant, and he made a note of it in his case records. Since there was no facility in Kozhikode during that period to tackle such complex cases and Sri KPK Menon wanted the best treatment possible, Dr. Menon fixed an appointment with Dr. H B Stallard at Moorefields Eye Hospital, London.

On meeting Dr. Stallard, Dr. Menon gave the case reports to him, and he examined Sri KPK Menon and cataract surgery was done very soon in one eye. It was Intracapsular cataract extraction. On the first postoperative examination, there was no vision improvement and Dr. Stallard noticed a Total Retinal Detachment. It was then that Dr. Stallard went through the notes written by Dr. Menon, and it was then that he noticed the mention of a Retinal detachment in one quadrant. He came in a hurry to Dr. Menon, who was in the waiting area, and said: "I apologise to you Dr. Menon, I didn't go through your clinical notes completely. He has a total RD. How did you make out the RD? "Dr. Menon replied that he used the torch light to check the pupillary reactions and checked the Projection and did a dilated fundus examination using the direct ophthalmoscope and assumed that there was a retinal detachment in one quadrant. Dr. Stallard repeated his apology thrice. He then asked Dr. Menon," Shall we change Horses? 'and he himself made arrangements to send Mr. KPK Menon to Dr. Shapland in France who did the RD surgery. But unfortunately, Mr. KPK. Menon did not regain vision. Later, He developed RD in his other eye too and he became bilaterally blind.

This incident highlights the magnanimity of Dr. Stallard, the other facet of a great athlete, author, and an ophthalmic surgeon par excellence.

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The indirect effect of emerging infectious diseases such as coronavirus disease 2019 on myopia progression

Dear Sir,

This is to bring an important global issue to the attention. Myopia is a remarkable global public health and socioeconomic crisis.[1-7] East Asia, and other regions of the world to a lesser scope, has been affected with a rising prevalence of myopia.[8,9] Based on the prevalence data and the corresponding population figures worldwide, more than half of the world population is anticipated to be myopic by 2050.[1,2,10] In addition to the cost and public health significance, this will hugely impact on quality of life and individual productivity of the affected people.[1,2]

In recent years, emerging infectious diseases (EIDs) such as coronavirus disease 2019 (COVID-19) and influenza A virus subtype H1N1 have become rising dangers to public health on a global level[11] enforcing people to be quarantined indoor.[1,2,12] This consequently results in home confinement during the pandemic thereby increasing time spent on near work and increased screen time at home.[1,2,12]

The COVID-19 pandemic has also enforced many educational systems to reflect on alternative methods such as remote electronic learning strategies.[2] Since the resultant behavioral and health significance of electronic learning have not been properly studied, it may be posing adverse risks for individuals, especially young children whose sensory functions are maturing through critical development.[1,2] This is for the fact that increased electronic learning involvement with digital screens and reduced outdoor activities are known as undesirable risks for myopia development.[1,2,13]

The outbreak and spread of the COVID-19 pandemic are substantially impacting people's lives by reshaping daily physical and learning behaviors.[2,13] This will add up to an already global vision crisis.[2,13,14] Since these EIDs are continually developing worldwide, they are expected to impact on the behavior of people pressurizing them to stay more often at home and this is going to come about quite often in the future.[1-3] Therefore, this will add more chances of getting myopia in the future due to the association of myopia progression and near work imposed by home confinement.[1,2] Children's refractive errors are more sensitive to environmental changes than older ages.[1,12] Thus, home confinement will impact more on young children.[1-3]

Since the inadequate time spent outdoor[1,2,12,15,16] and increased duration and intensity of near work activities[1,2,12,17,18] have been found as chief environmental risk factors for myopia progression, home confinement will lead to the development of the myopic crisis further.[1-3]

The outstanding upward trend for the development of myopia coincides with the age at which schooling with rigorous near work activities begins.[1,2,18,19] As a result, it is imperative to consider the influence of home confinement in the development of myopia particularly in school-aged children while they are in quarantine, and then suggest essential measures to protect them against the progression of myopia.[1-3]

That is also important to know that axial elongation of the eye related to early myopia increases risks of other ocular diseases including macular degeneration, posterior staphyloma, retinal detachment, cataract, and glaucoma that could cause blindness.[1,20]

In addition, since myopia onset is becoming increasingly prevalent among young children, predominantly in urban regions[8,21,22] and for the fact that the earlier children become myopic, the more likely they develop high myopia, and the worse the prognosis,[23] myopia should be taken priority in health policies.[1,2]

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