All India Ophthalmological Society

Diagnosis and Management of

PRIMARY OPEN ANGLE GLAUCOMA

EDITOR

Dr. Tanuj Dada

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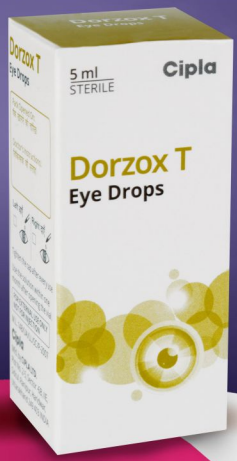

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For any suggestions, please write to
Hony. General Secretary
AIOS

Dedicated to

Dr. (Maj) Laishram Jyotin Singh

Ashok Chakra (Posthumous)

Major Laishram Jyotin Singh, born in 1972 in Manipur (India), was an army doctor in the Indian Army Medical Corps. He was commissioned in the Army Medical Corps in 2003, and was sent on deputation to the Indian Medical Mission in Kabul, Afghanistan in 2010. On 26th February 2010, a heavily armed suicide bomber attacked the guarded residential compound killing the owner and three security guards. Major Jyotin, unmindful of his own safety, confronted the terrorist with his bare hands and pinned him down such that he could not fire his AK-47 or lob grenades. At this point, the armed intruder detonated his suicide vest killing him instantaneously. Unfortunately Major Jyotin also got severely burnt and succumbed to his injuries. Major Jyotin displayed gallantry and commitment beyond the call of his duty and laid down his life to protect others in the highest traditions of the Indian Army. For his act of exemplary courage, valour and supreme sacrifice, he was awarded the "Ashoka Chakra" posthumously, the highest peacetime gallantry award in the Indian Armed Forces.

Jai Hind

Message from the
General Secretary

Dear Friends,

Primary Open Angle Glaucoma (POAG) is the leading cause of irreversible blindness in India. A large majority of patients remain undetected and early signs of glaucoma are often missed during routine ophthalmology examination.

There is an unmet need to educate general ophthalmologists in the diagnosis and management of POAG and it gives me great pleasure to bring to all AIOS members, a great educational resource on POAG.

This is a publication from the National Glaucoma Expert group and offers Consensus Statements, management algorithms and a unique case-based learning for every eye care practitioner.

I wish to thank all the participants who have taken out time to provide their knowledge and experience which has been condensed into this monologue. I wish to thank Cipla for funding this educational endeavour and providing the logistics for holding the meeting.

I express my heartfelt gratitude to Prof. Tanuj Dada and the entire editorial team who have put in immense efforts to produce these guidelines in the most user friendly, yet comprehensive manner. This is a must read not only for all general ophthalmologists but also glaucoma experts and post graduate students.

We hope that you all will find this to be a useful and practical guide in your day-to-day clinical practice.

With Best Wishes,

Dr. (Prof.) Namrata Sharma
Honorary General Secretary
All India Ophthalmological Society

Message from the Treasurer

Dear Friends,

The All India Ophthalmological Society leads the way in ophthalmic education for all its members. This consensus publication from the AIOS glaucoma expert group serves as a useful guideline for the general ophthalmologists to manage patients in their clinical practice.

To create such guidelines in Primary Open Angle Glaucoma (POAG), notable experts in the field of glaucoma from the entire country were invited. A detailed questionnaire was prepared related to the understanding of the clinical condition and the management protocol of the same. It was then put forward to each glaucoma expert present in the meeting. There was a detailed discussion on each issue and a consensus was arrived at every point. This was then converted in the form of guidelines, reviewed by separate national and international experts of high repute and sent for publication. I would like to appreciate and thank Prof. Tanuj Dada for all the efforts that he has put in preparing this consensus guideline for managing open angle glaucoma.

I hope that the efforts of all the glaucoma experts of the country and AIOS will be of immense use for the practicing ophthalmologists in managing cases of open angle glaucoma. We are ready with guidelines related to other ophthalmic conditions as well and we have already planned for more focused group meetings and consensus guidelines on various ophthalmic disorders in future.

I wish you all a very happy new year 2020 and wish good luck and fortune for all your future endeavours. May you succeed in everything in life and attain great happiness and well-being.

Best regards,

Dr. (Prof.) Rajesh Sinha
Hony. Treasurer
All India Ophthalmological Society

AIOS Guidelines on Primary Open Angle Glaucoma

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Editorial

Glaucoma is the leading cause of irreversible blindness worldwide. It is critical to diagnose the disease at an early stage and initiate appropriate therapy to prevent blindness. The current guidelines for diagnosis and management of Primary Open Angle Glaucoma (POAG) outline the practical aspects of managing glaucoma patients with focus on the diagnosis of an open versus closed angle on gonioscopy, picking up early signs of glaucomatous optic neuropathy on clinical evaluation and setting of target IOP to medically manage a glaucoma patient. Several case studies have been included to facilitate learning and simple algorithms are presented to optimize the therapeutic management. We hope that this module compiled with the collective wisdom of top glaucoma experts of the country will provide an easy reference text to help ophthalmologists in taking care of glaucoma patients.

We would like to express our heartfelt gratitude to Chief R.P. Centre, **Prof. Atul Kumar** for his constant support and guidance.

Editorial Committee

CONTENTS

Summary: Management of a Glaucoma Patient

History	
Demographic data	Name, date of birth, gender, race, income, medical insurance
Chief complaints	Coloured haloes, redness, pain, blurred vision, peripheral field loss
Ocular history	Baseline IOP (untreated), how patient instils eye drops Number of medications used (systemic , topical, inhalational) Timing of medication use, time gap between 2 medicines Adherence to treatment, eye drop administration (self/caregiver) Previous use of any form of steroids , history of blunt trauma, any recent stressful event, Any laser/surgery performed previously
Systemic history	Systemic illnesses: Diabetes mellitus, hypertension (check BP), cardiac illness, carotid occlusive disease, autoimmune diseases, migraine, dementia, dyslipidemia, asthma/ COPD, obstructive sleep apnoea, chronic kidney disease, arthritis, cerebrovascular disease, depression, Raynauds disease, prostrate disorder, constipation, sexual dysfunction Systemic medications: Especially Steroids, beta blockers, psychotropic drugs (TCAs, anti-psychotics, topiramate), anticoagulants, tamsulosin
Family history	History of glaucoma or glaucoma blindness in first or second degree relatives (get entire family of glaucoma patient screened)
Personal/ occupational history	Driving status, exercises (yogic postures involving Valsalva manoeuvre), excessive water intake in morning, smoking, alcohol, tight neck-tie wearing, excessive weight lifting/ trumpet blowing/ scuba diving
Clinical Examination and Investigations	
Best corrected distance and near visual acuity	
Pupillary reactions – document RAPD	
Intraocular pressure – mention time of measurement (GAT is the preferred technique)	
Central corneal thickness (don't write corrected IOP, just mention CCT)	
Slit lamp examination – eyelids, ocular surface, can perform TBUT when you instil fluorescein for GAT, Peripheral and central AC Depth, cornea, iris, anterior chamber, lens, + 90D biomicroscopy	
Gonioscopy is essential to document type of glaucoma- record angle structures visible	
Dilated stereoscopic fundus examination, colour and red free fundus photography, draw a disc diagram and note vertical cup-disc diameter ratio, RNFL defects, notching, disc hemorrhage	
Visual fields are essential, Do RNFL OCT if available esp. in glaucoma suspects, early glaucoma	
Diagnosis and treatment	
Stage the disease: Early, Moderate or Advanced (rule out angle closure, check for PDS, PXF)	
Set Target IOP Early POAG: 16-18mmHg Moderate POAG: 14-16mmHg Advanced POAG: ≤12mmHg	
Initiate topical therapy (rule out drug allergy, check for interactions with systemic medications)	
Regular life long follow-up (check disease progression, drug side effects, any new co-morbidity)	
Patient counselling	
Diagnosis	Discussion about the disease, its current stage and natural course
Treatment	Life-long therapy and Importance of regular and timely follow-up Common side-effects of medications (laser/surgery) Technique of using eye drops, phone alarm to remember time Modification of therapy in breastfeeding/ pregnant women
Lifestyle modification	Regular aerobic exercise, meditation, diet rich in green leafy vegetables, avoid head down Yoga posture, stop driving (advanced visual field damage affecting both eyes), quit smoking, use LVA (low vision aids - visual field expanders)

There are two key skills required for the diagnosis of Glaucoma.

- Gonioscopy to distinguish an open angle versus a closed angle
- Evaluation of the retinal nerve fiber layer & optic disc to pick up early signs of glaucomatous damage.

Starting from the root of the iris, the following structures are present in a normal adult angle:

1. Ciliary body band
2. Scleral spur
3. Pigmented trabecular meshwork
4. Non-pigmented trabecular meshwork
5. Schwalbe's line.

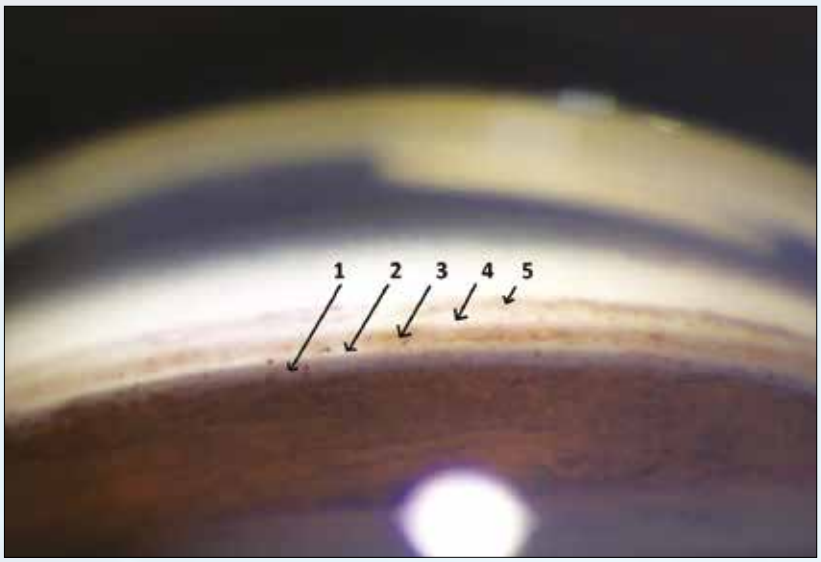


Figure 1a: Open Angle showing all angle structures-
1: Ciliary body band;
2: Scleral Spur;
3: Posterior pigmented trabecular meshwork;
4: Anterior non-pigmented trabecular meshwork;
5: Schwalbe's line.

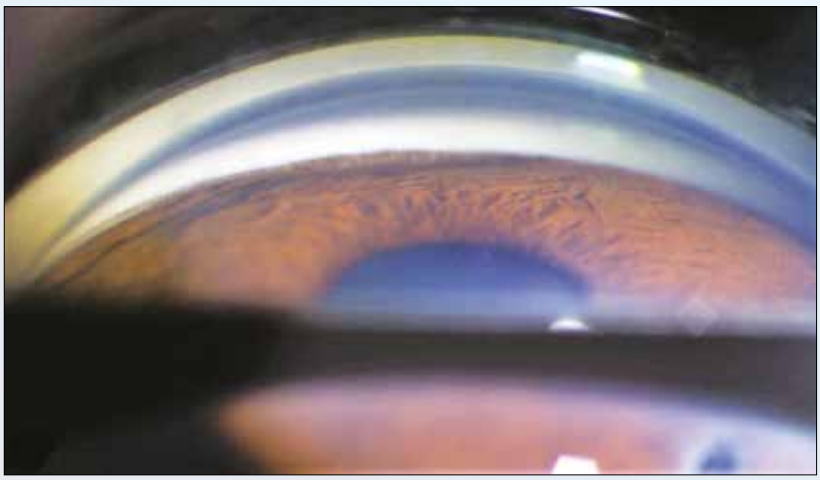


Figure 1b: Closed angle on Gonioscopy. Angle Structures are not visible in primary gaze.

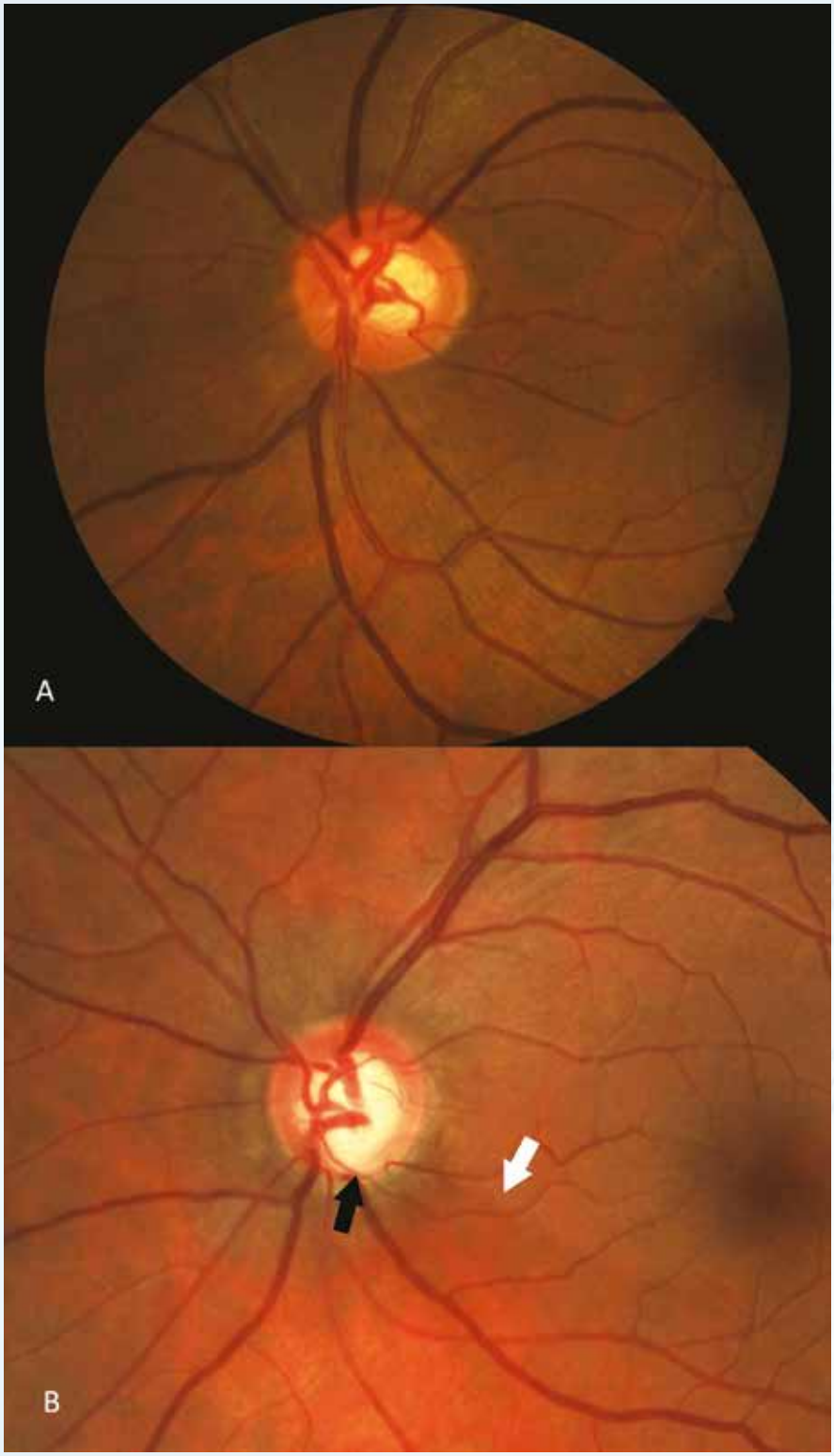


Figure 2: (A) Normal average-sized optic nerve head with physiological cupping; (B) Glaucomatous cupping with Inferior Notch (black arrow) and RNFL defect (white arrow)

Online access for basic course in Glaucoma by **World Glaucoma Association** @ https://wga.one/wga/basic-course-in-glaucoma/

Section - I

PHOTO ATLAS

Gonioscopic Identification of Open versus Closed Angle

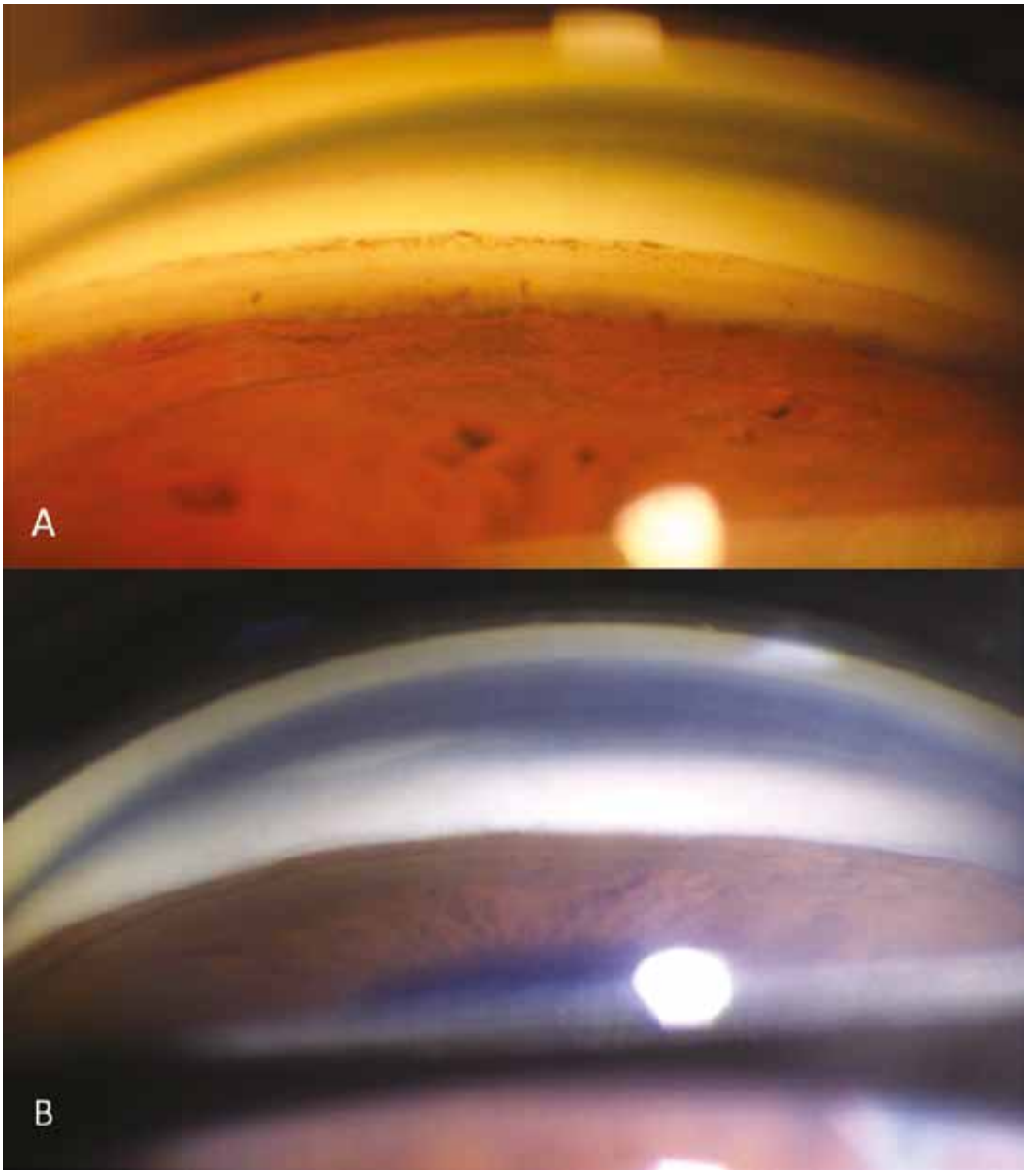


Figure 3: Open angle (A) versus Closed angle, (B) on gonioscopy.

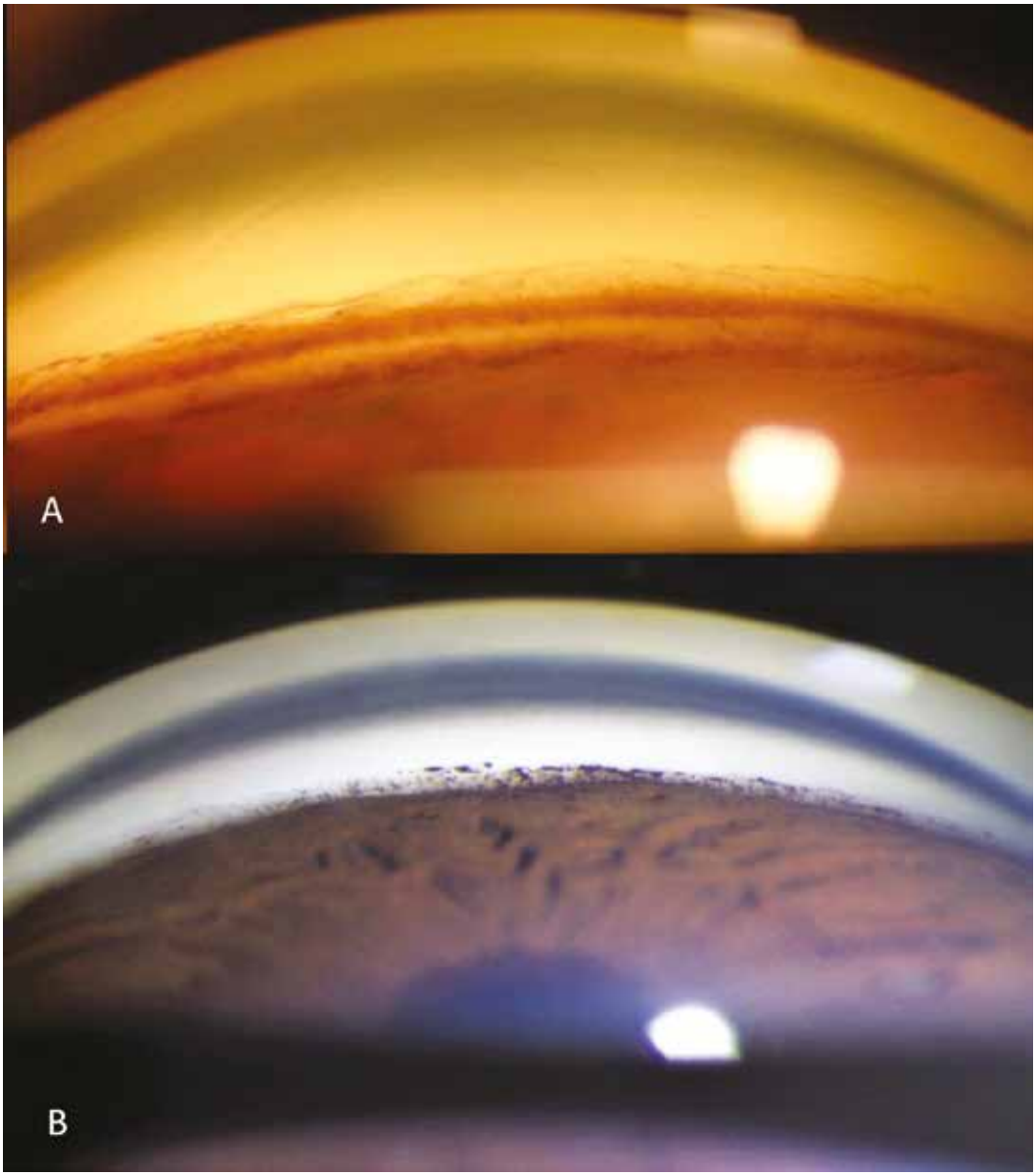


Figure 4: (A) Open angle; (B) Closed angle on gonioscopy.

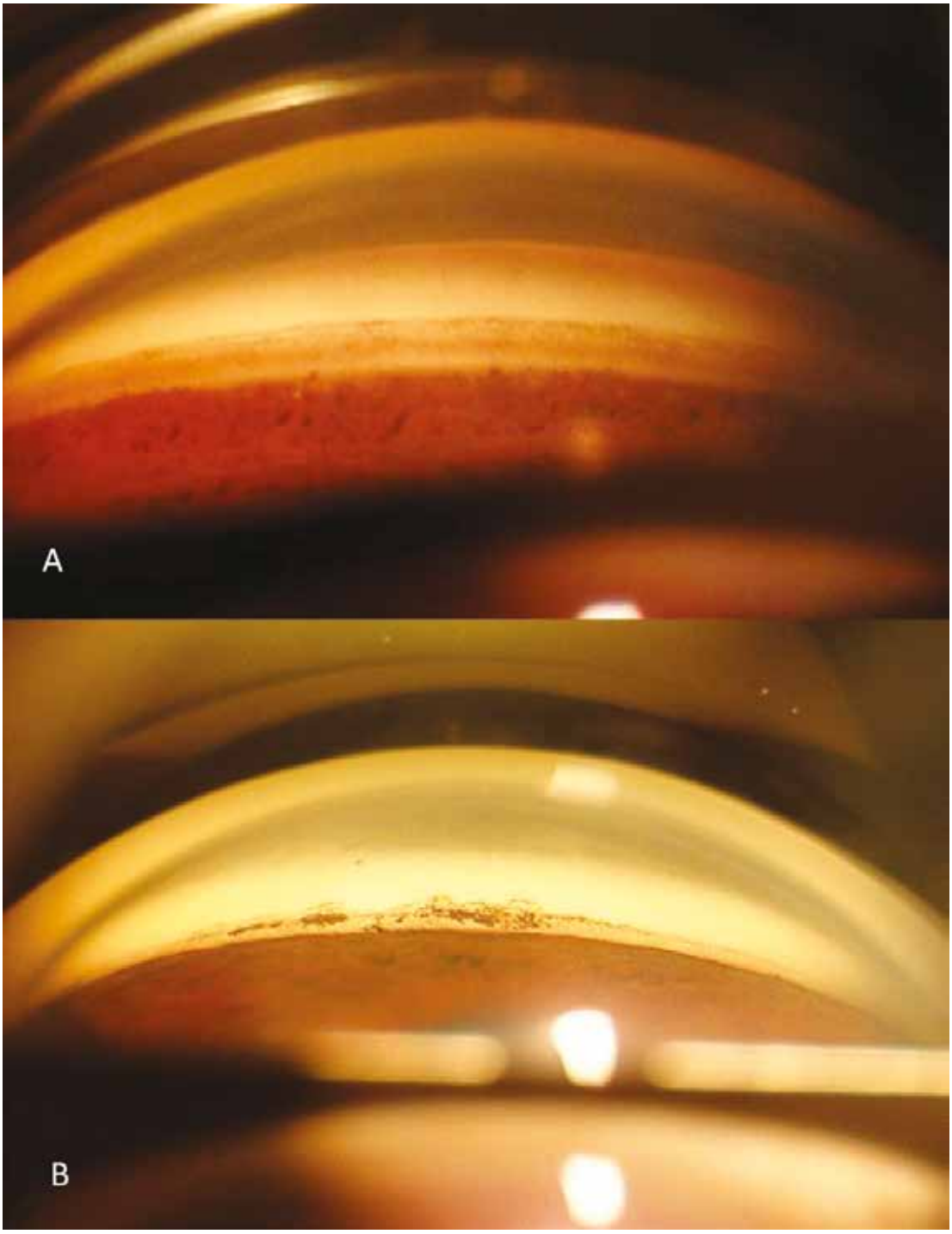


Figure 5: (A) Open Angle; (B) Closed angle with blotchy pigments at the Schwalbe's line.

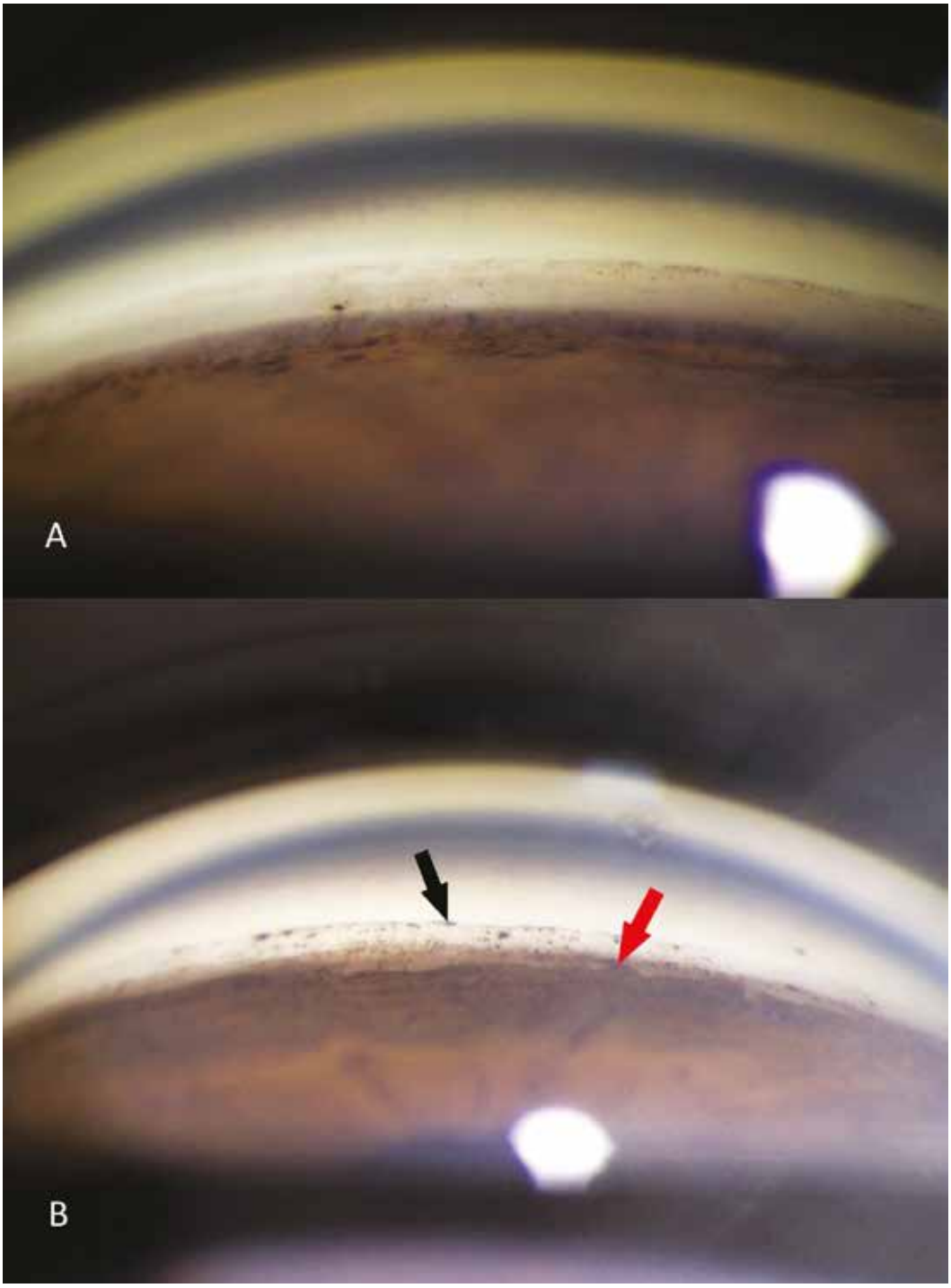


Figure 6: (A) Open Angle; (B) Closed angle with goniosynechiae (red arrow) and blotchy pigments at the Schwalbe's line (black arrow)

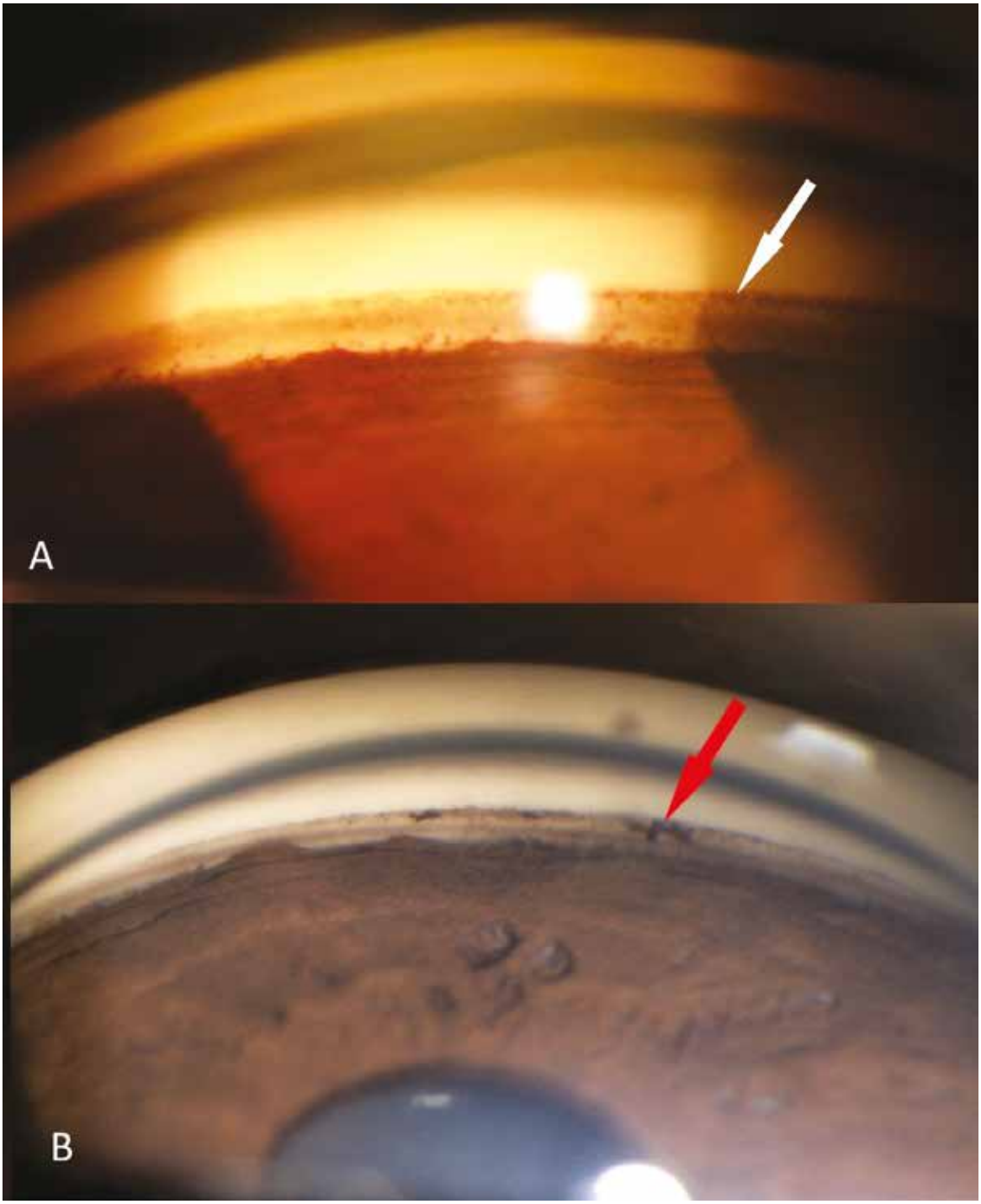


Figure 7: (A) Open angle with fine pigmentation over Schwalbe's line in inferior angle (white arrow); (B) Blotchy pigments (red arrow) and goniosynechiae (irido-trabecular adhesions) in Primary Angle Closure.

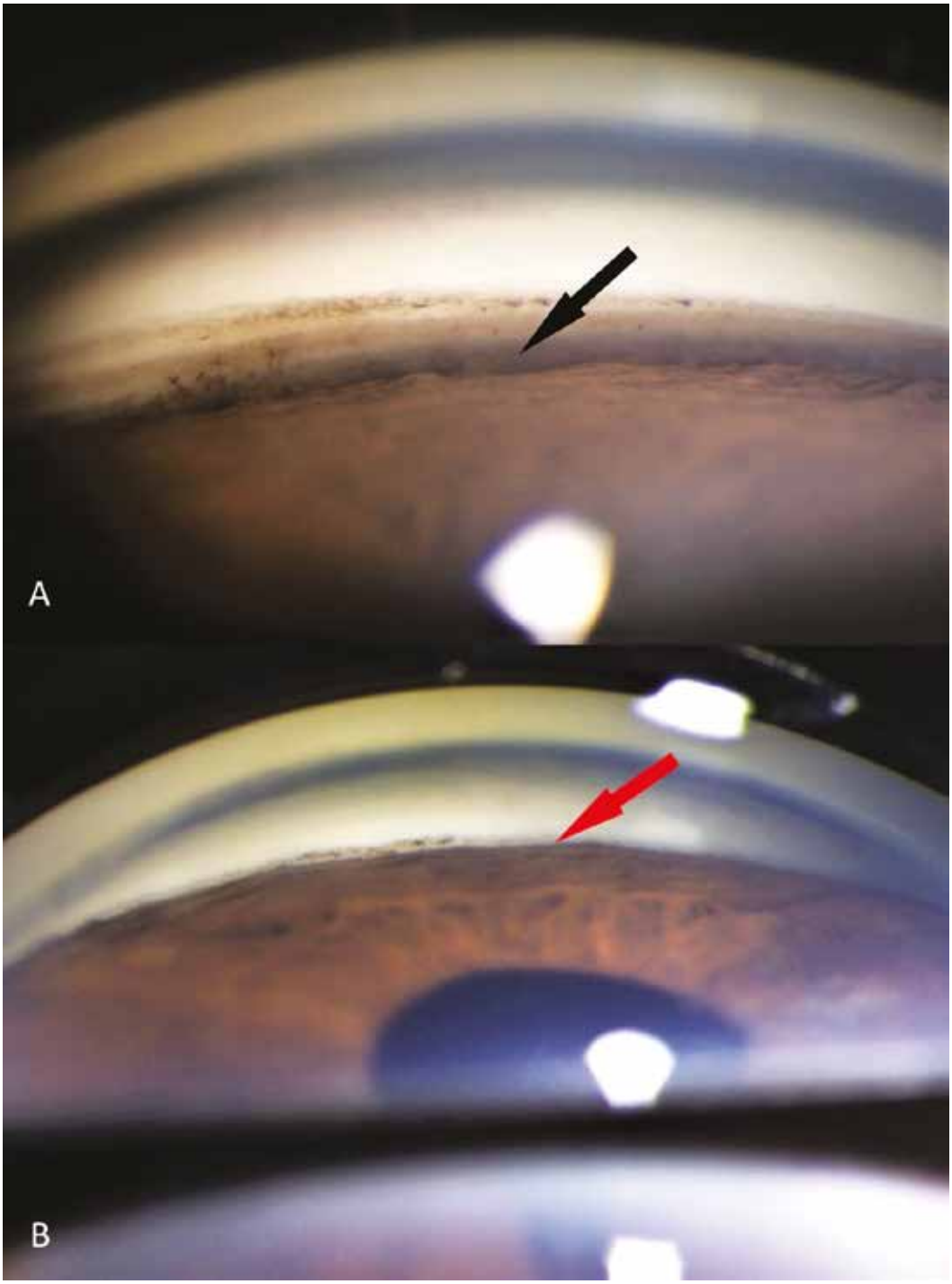


Figure 8: (A) Open angle upto ciliary body band (black arrow); (B) Complete angle closure (red arrow) no angle structures visible.

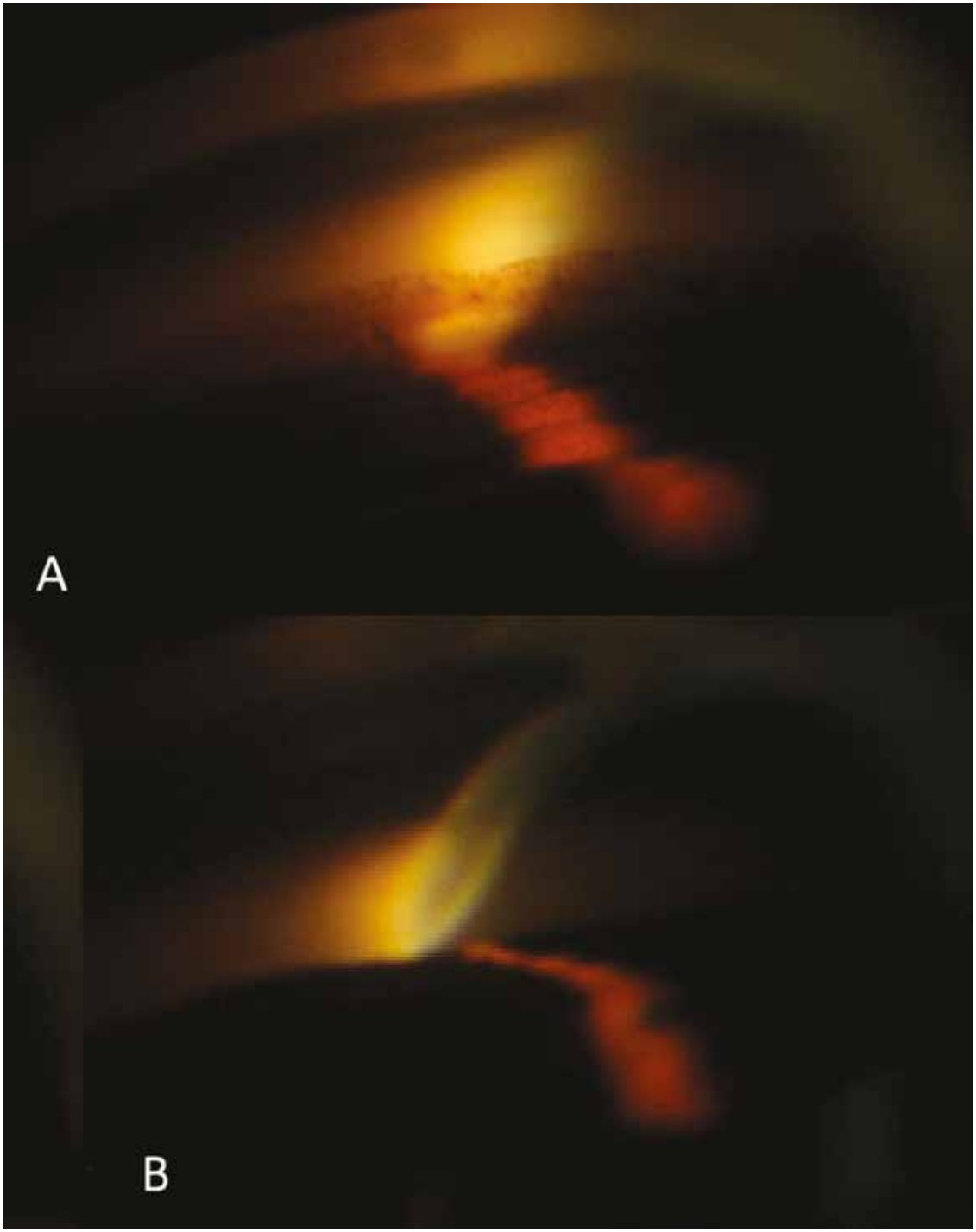


Figure 9: Utility of corneal wedge and iris configuration in identification of Open versus Closed angle on primary gaze in gonioscopy. (A) Wide open angle with flat iris configuration and angle structures visible beyond corneal wedge. (B) Angle structures not visible beyond corneal wedge, convex iris configuration in angle closure.

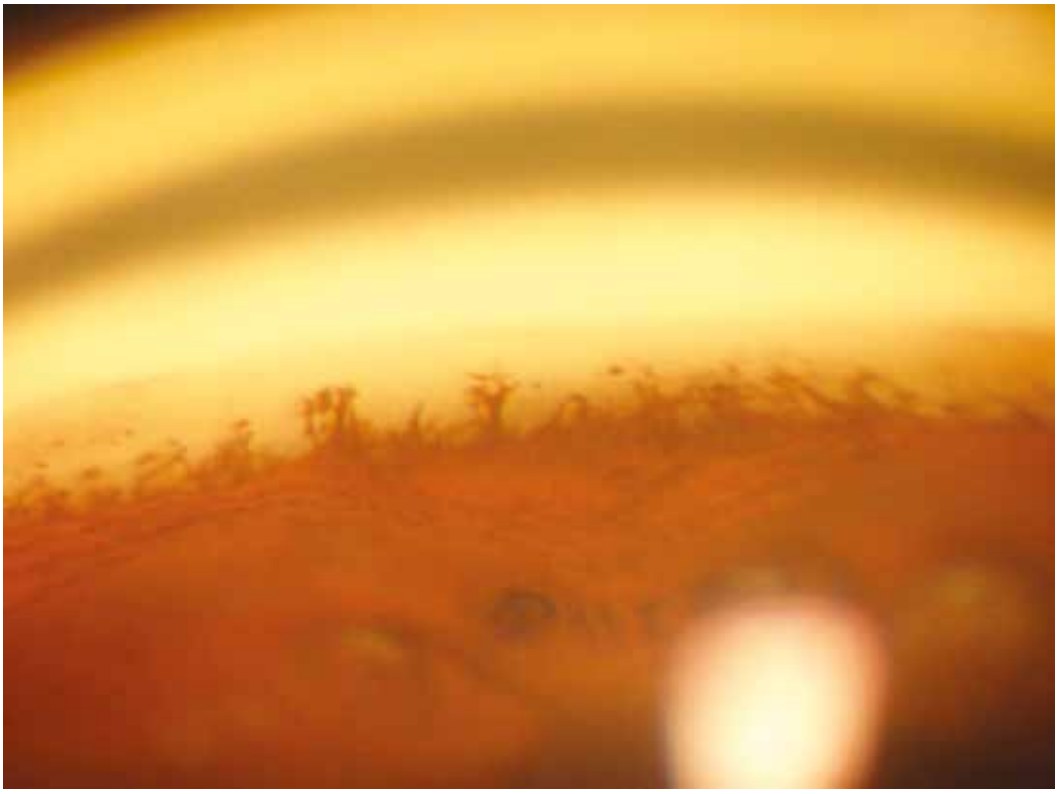


Figure 10: Open angle with prominent iris processes in Juvenile Open Angle Glaucoma (JOAG).

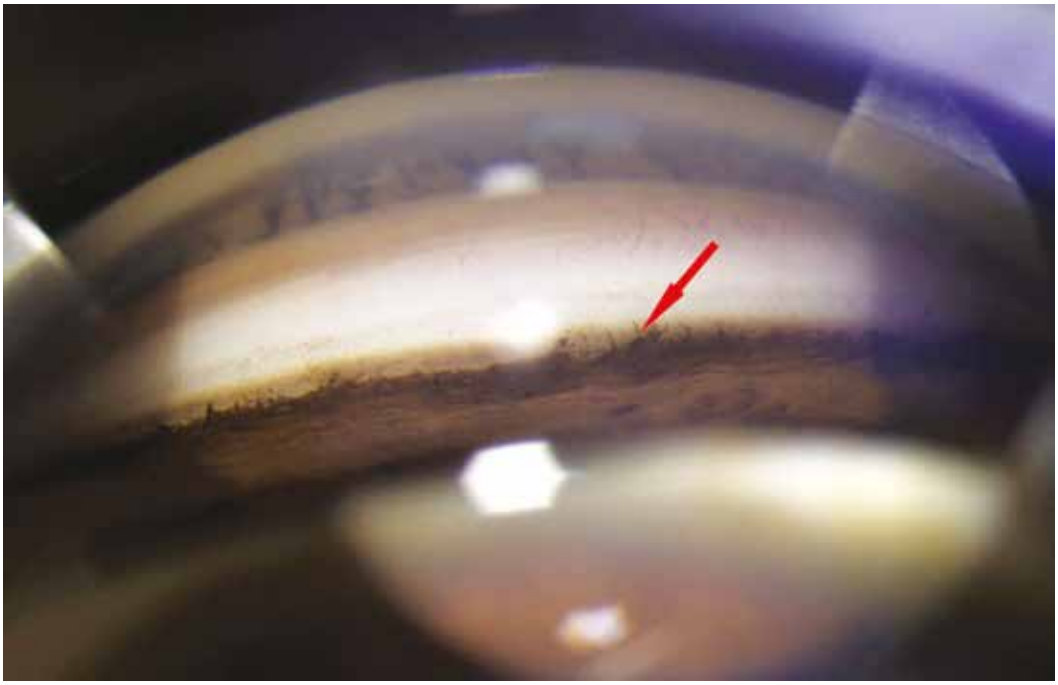


Figure 11: Anterior insertion of Iris over trabecular meshwork in JOAG (red arrow).

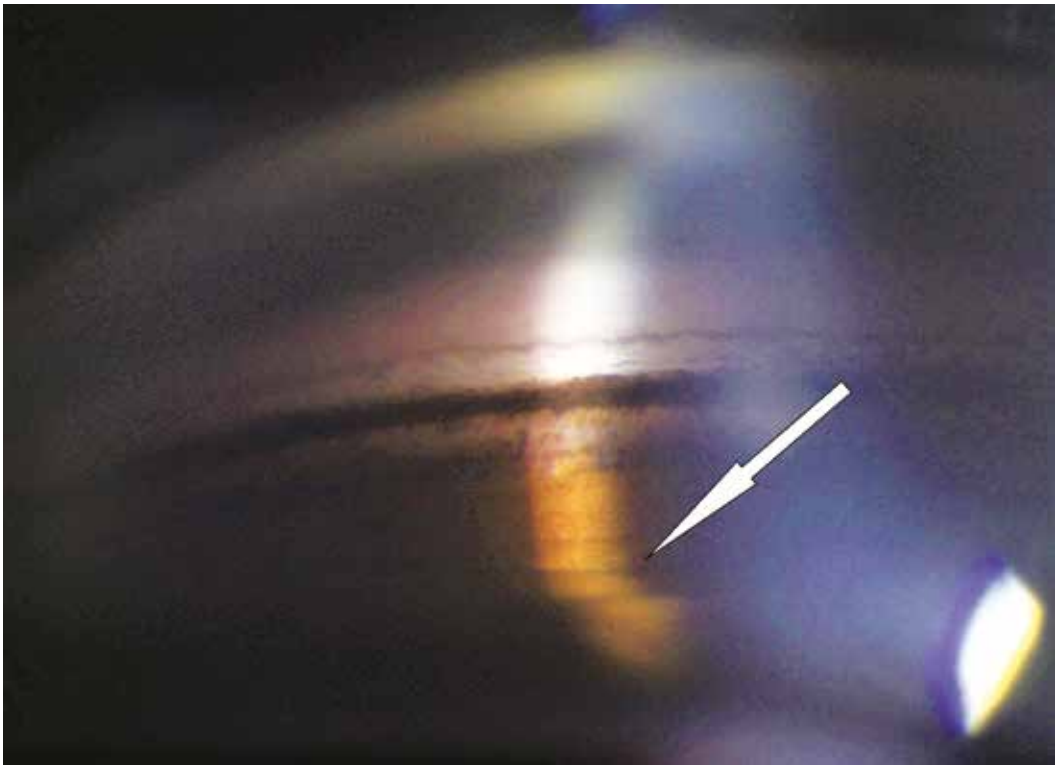


Figure 12: Band-like pigmentation at trabecular meshwork with concave iris configuration (white arrow) in Pigment dispersion syndrome.

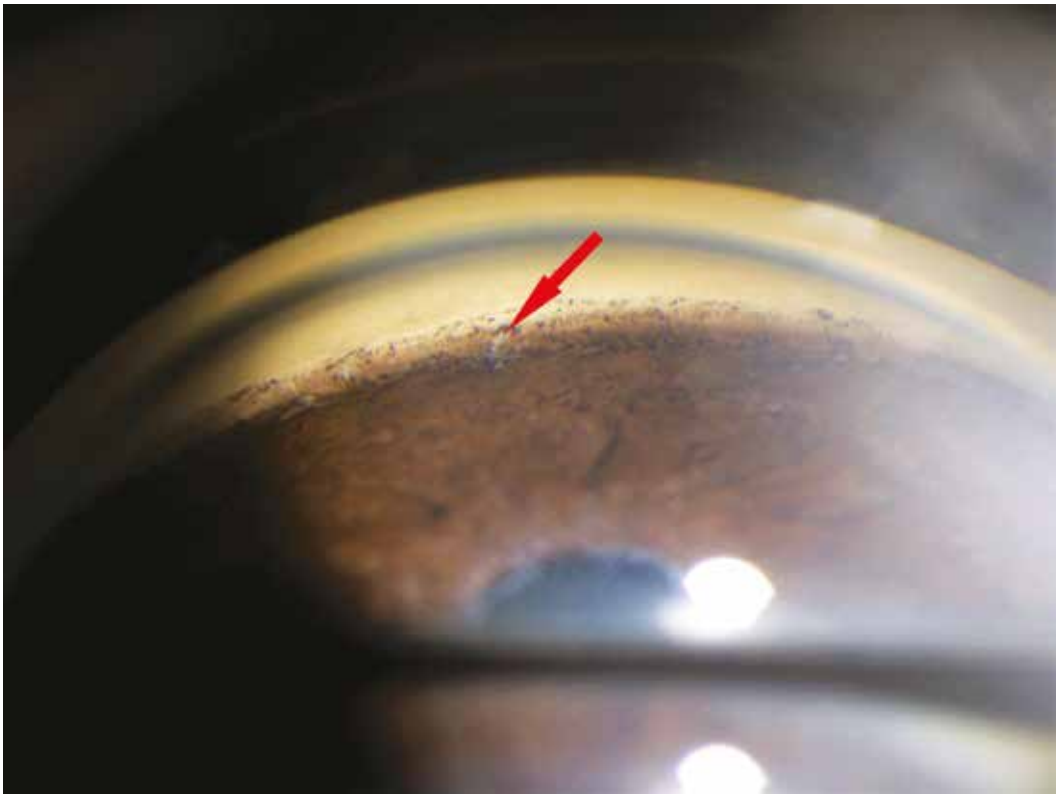


Figure 13: White flecks-like material deposition in the angle in Pseudoexfoliation (red arrow).

Optic Nerve Head Evaluation

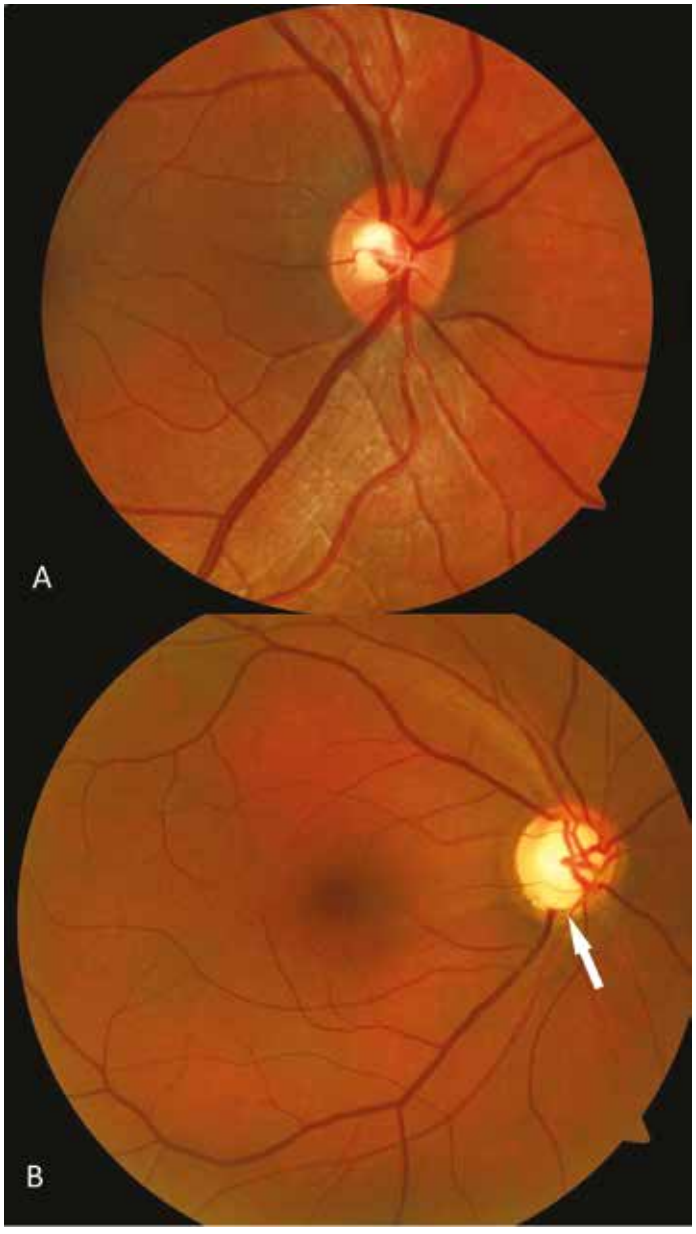


Figure 14: (A) Normal, average-sized Optic nerve with healthy neuroretinal rim (NRR); (B) Glaucomatous optic neuropathy with inferior NRR loss with notch (white arrow); ISNT rule not followed.

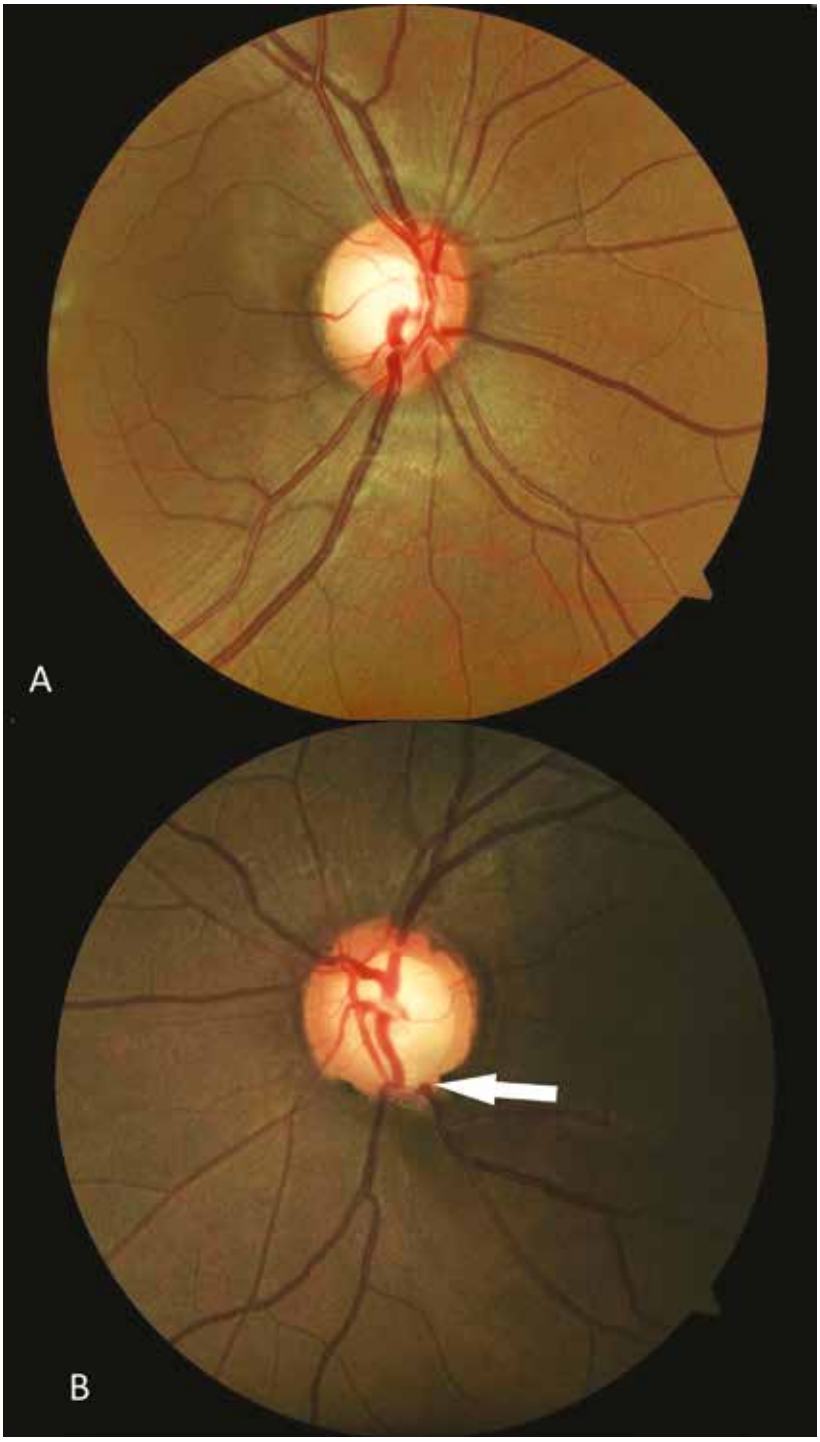
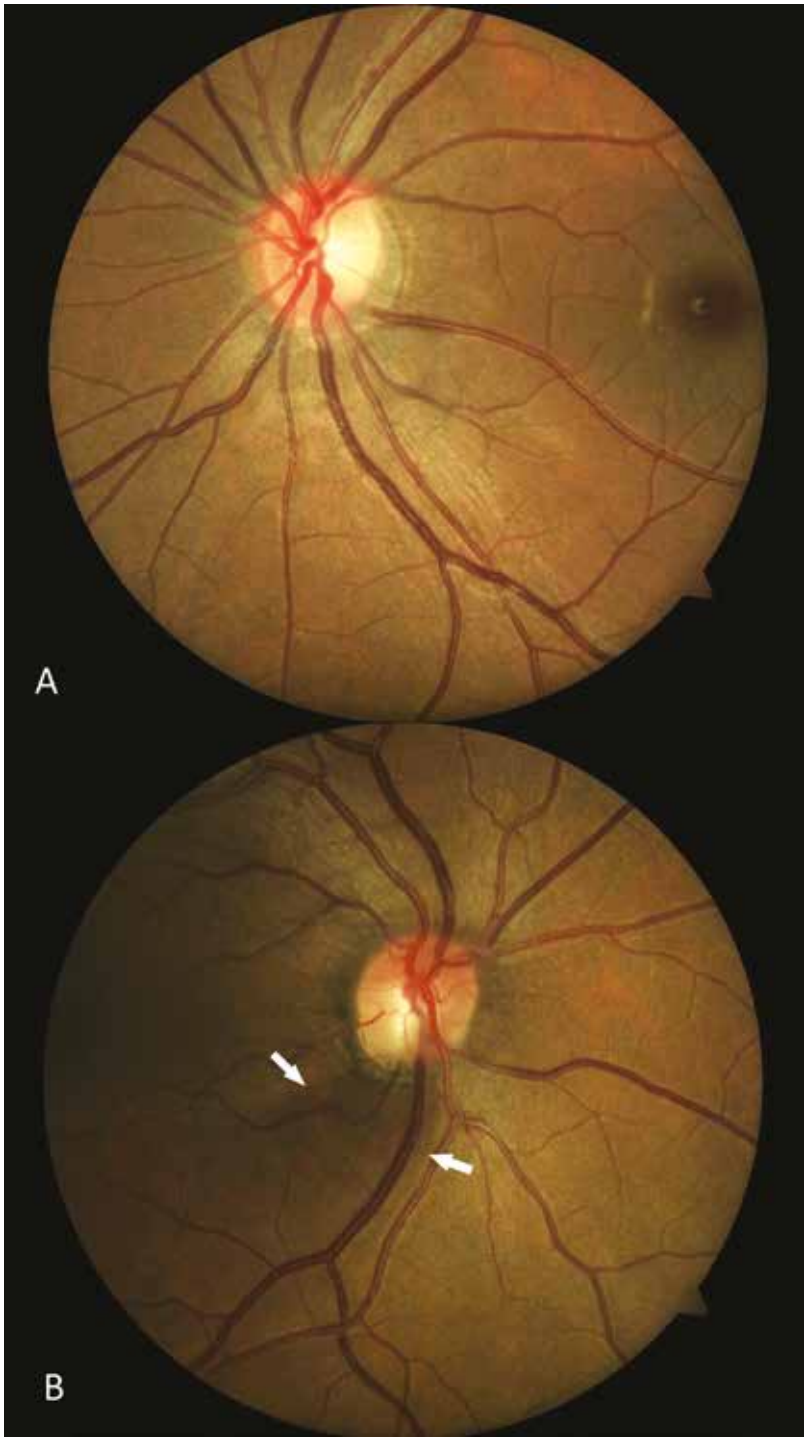


Figure 15: (A) Large optic nerve head with a physiological cup, normal NRR – ISNT rule is followed; (B) Large optic nerve with glaucomatous inferior loss of NRR with notch (white arrow)



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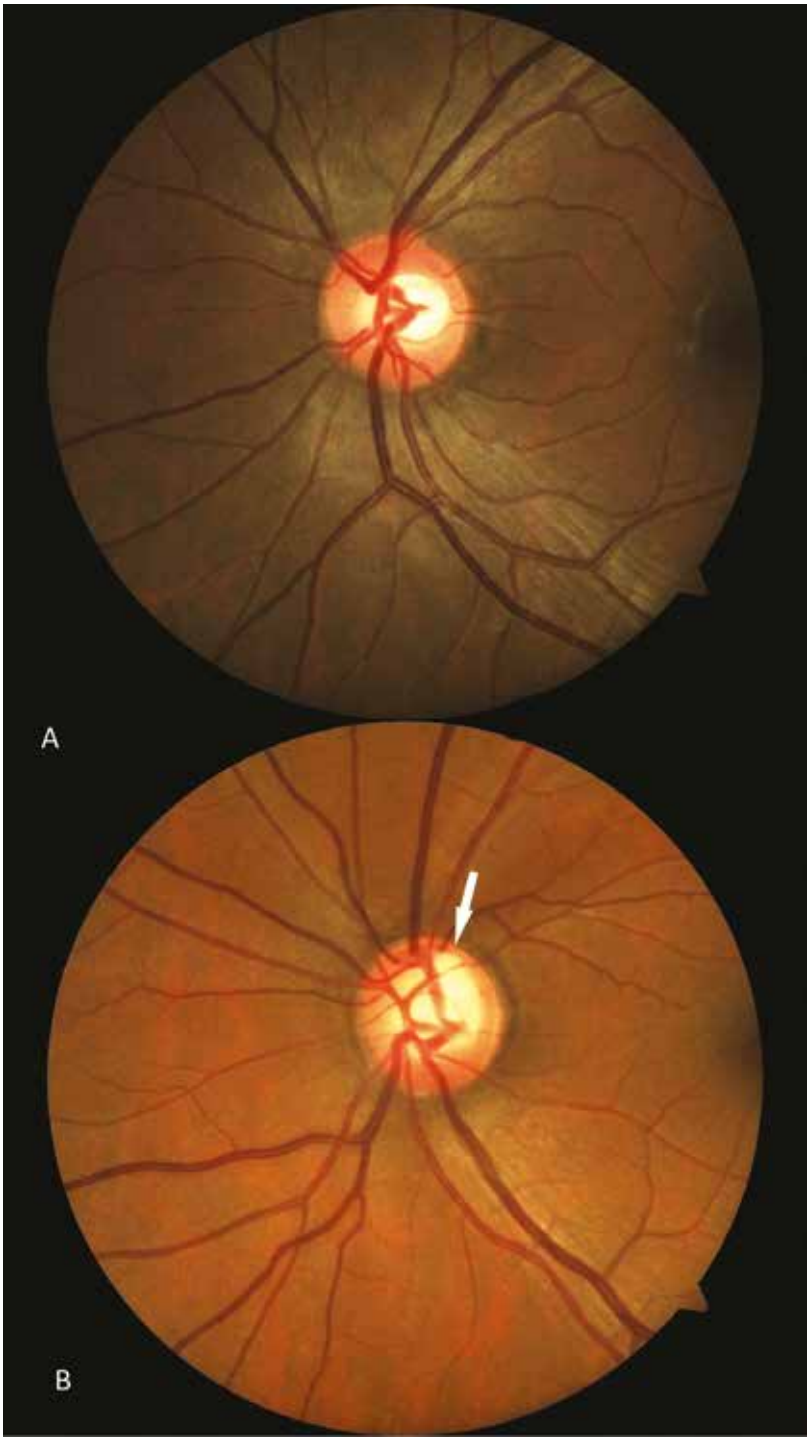

Figure 17: (A) Average-sized disc with healthy NRR; (B) Glaucomatous cupping with Superior Notch (white arrow).

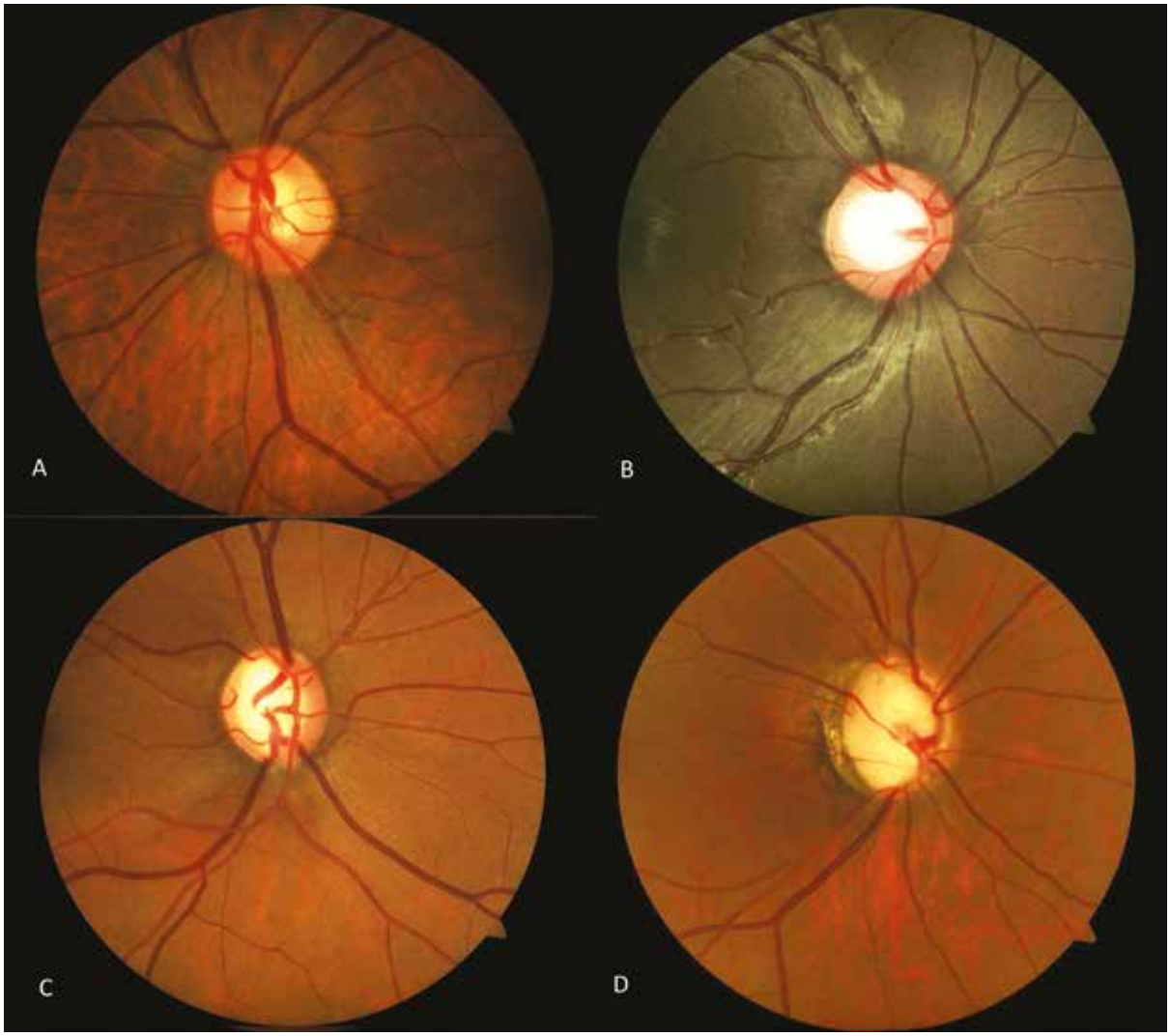

Figure 18: (A) Average-sized normal optic nerve head. (B) Large optic nerve with physiological cupping; (C) Inferior and superior NRR notch and CDR of 0.8- 0.9:1; (D) Near total cupping.

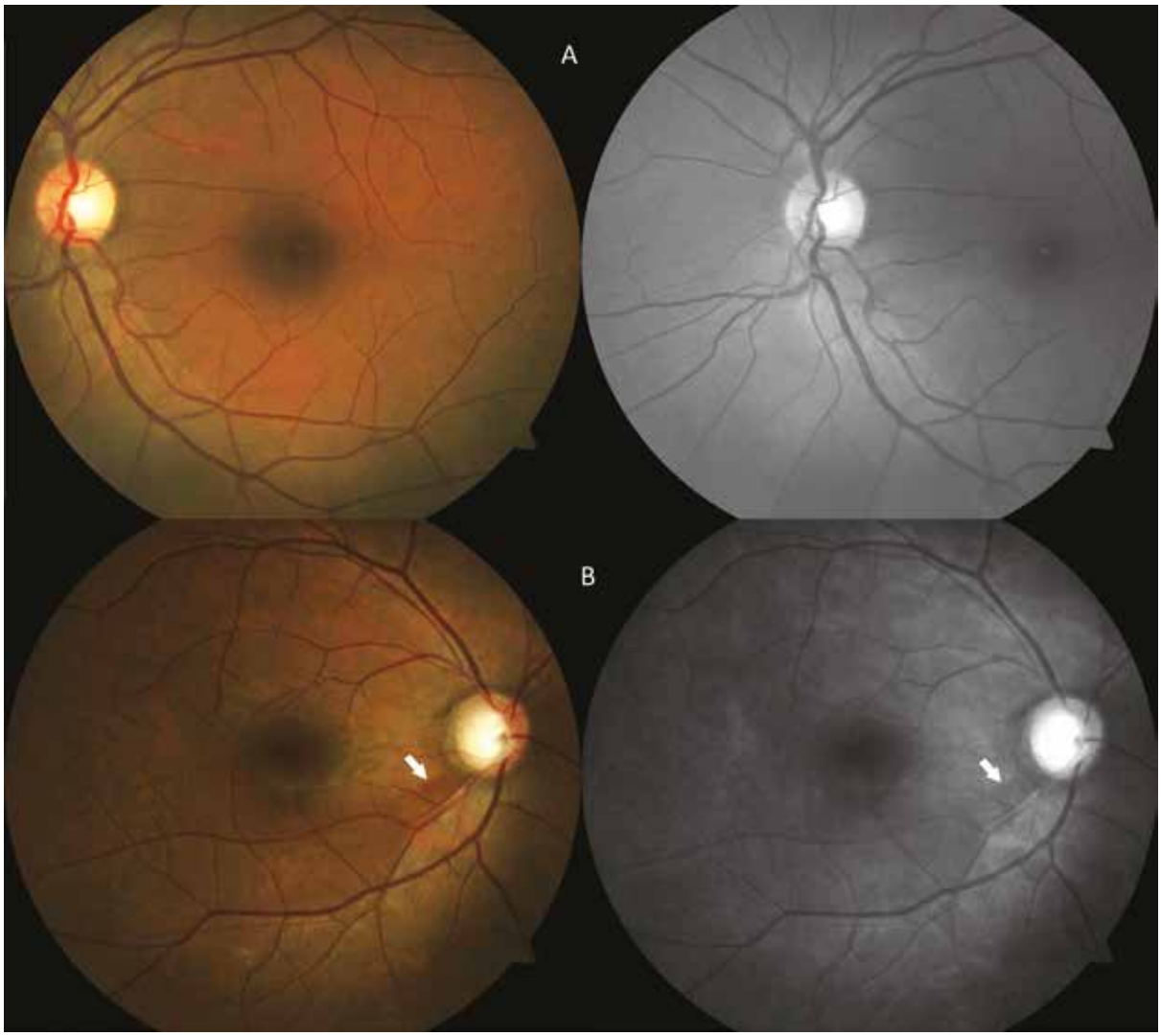

Figure 19: Colored and red free fundus photograph (A) Average-sized disc with normal RNFL; (B) Average-sized disc with increased vertical cup:disc ratio with wedge shaped RNFL defect (white arrow).

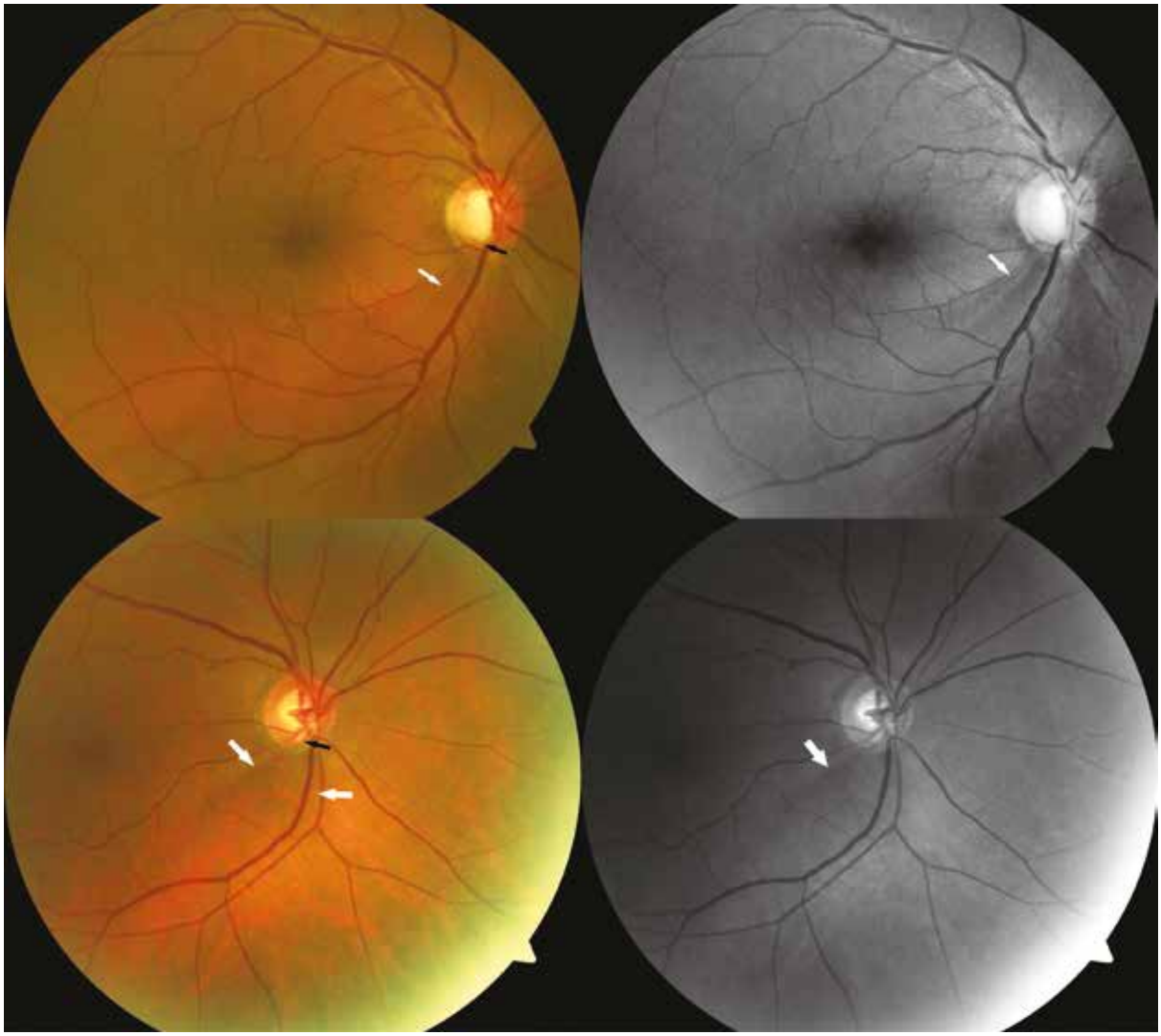

Figure 20: Inferior RNFL defects (white arrow) with inferior notch (black arrow) with red-free images showing enhanced RNFL wedge shaped defects.

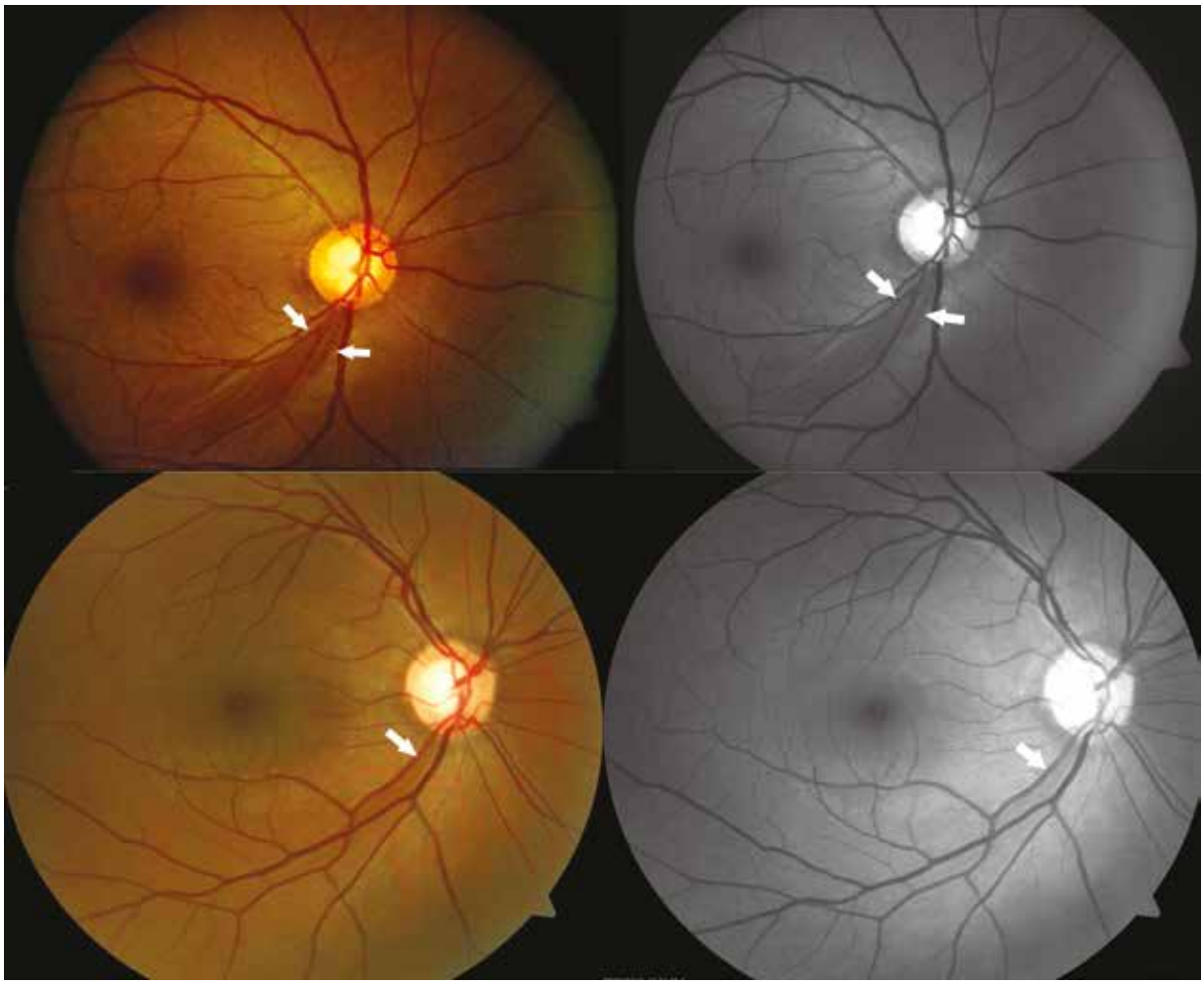

Figure 21: Early RNFL defects with small indiscernible notch in inferior NRR of optic nerve head.

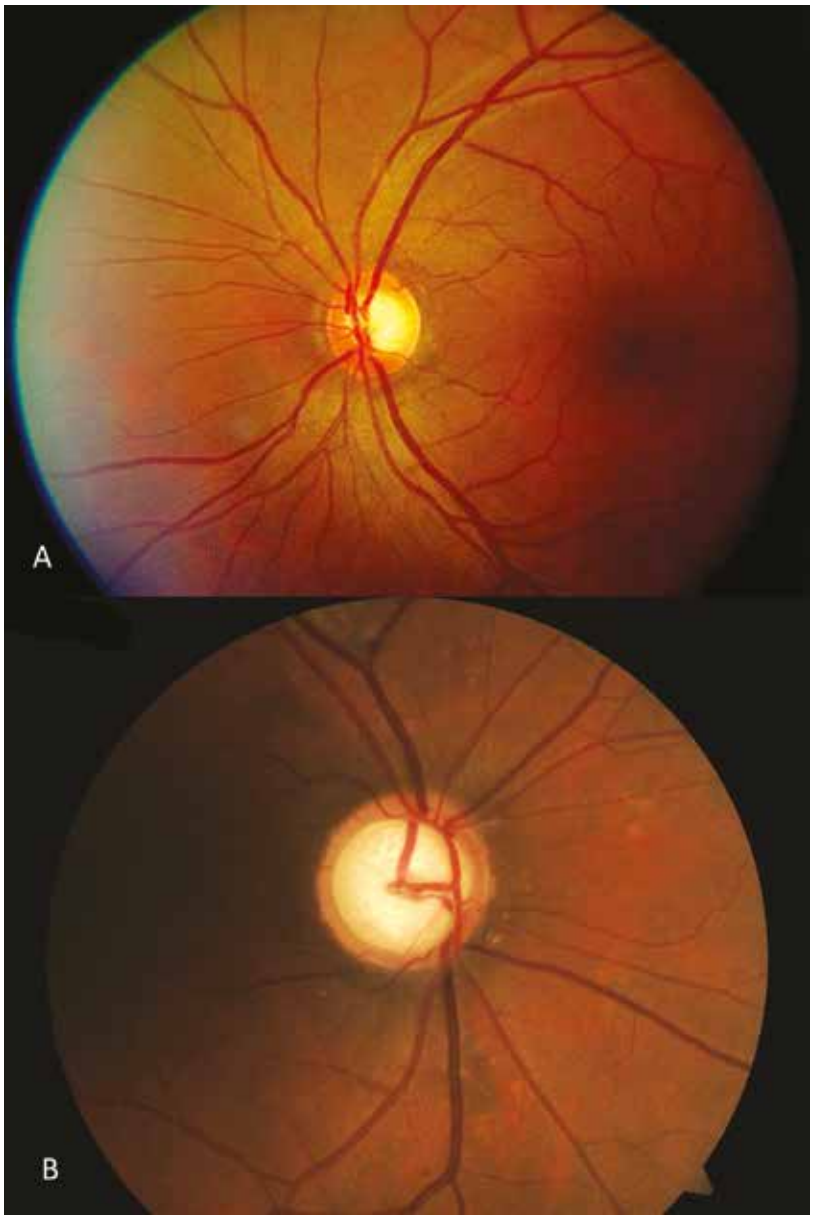

Figure 22: (A) Normal Optic disc with NRR following ISNT rule; (B) Concentric cupping in a JOAG.

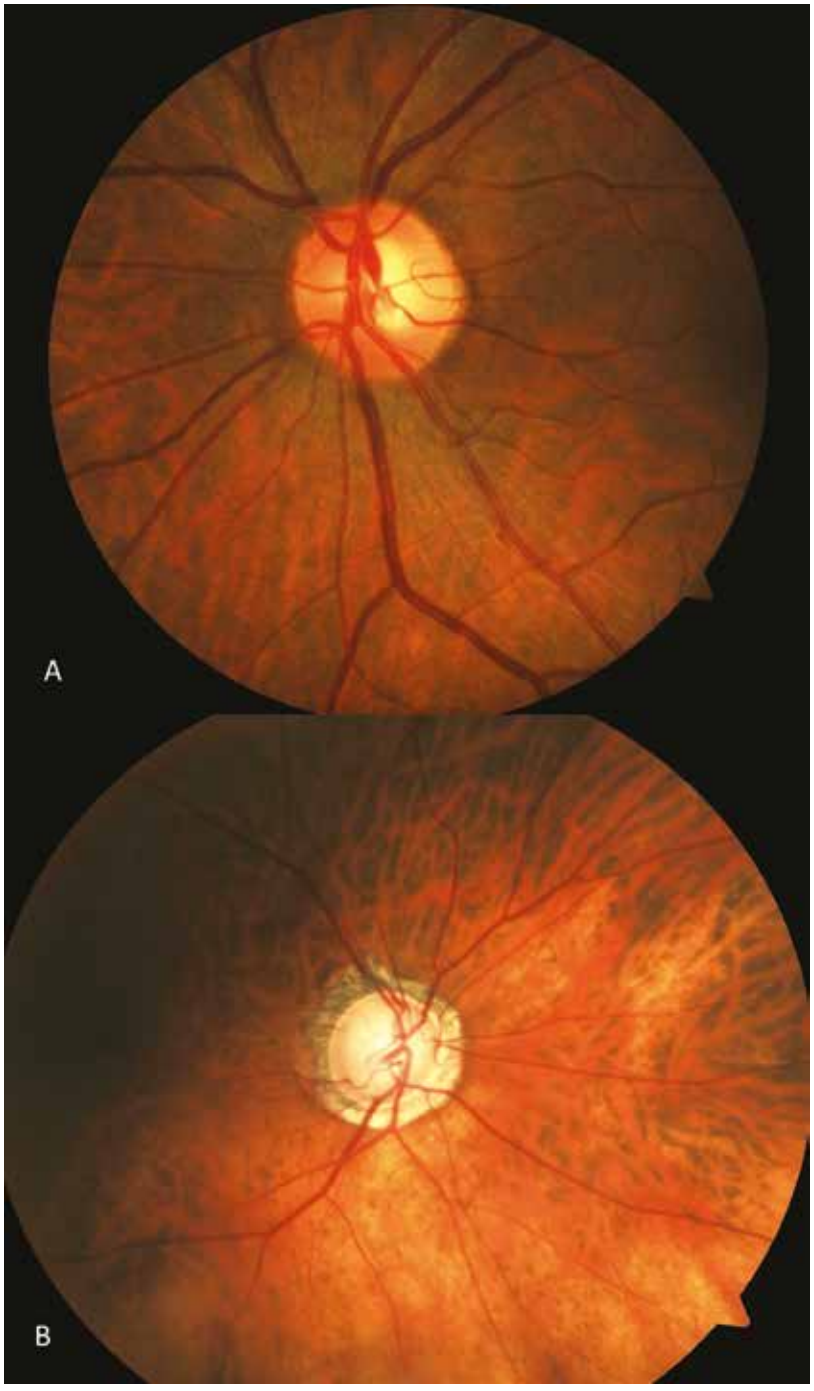

Figure 23: (A) Normal optic nerve; (B) Saucerisation with shallow near total cupping and 360 degrees peripapillary atrophy in a myopic patient with glaucoma

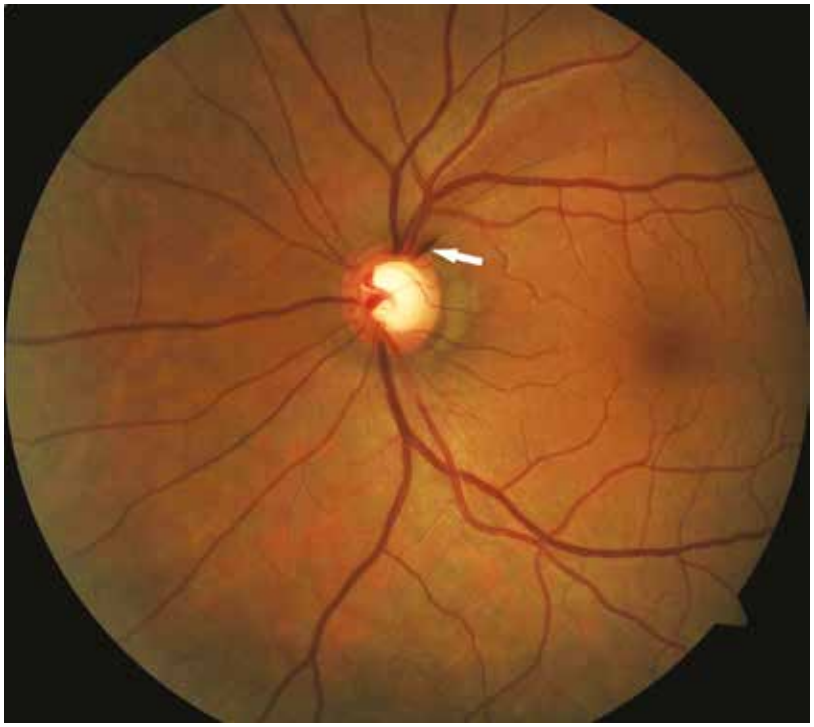

Figure 24: Optic nerve haemorrhage with RNFL defect (white arrow).

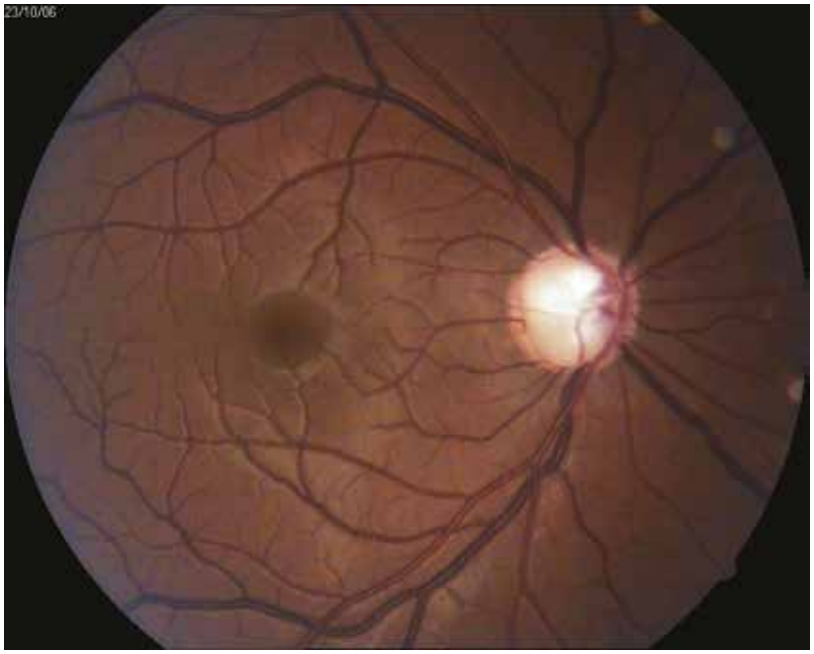

Figure 25: Bayonetting - sharp bending of vessels over the cup margin in advanced cupping.

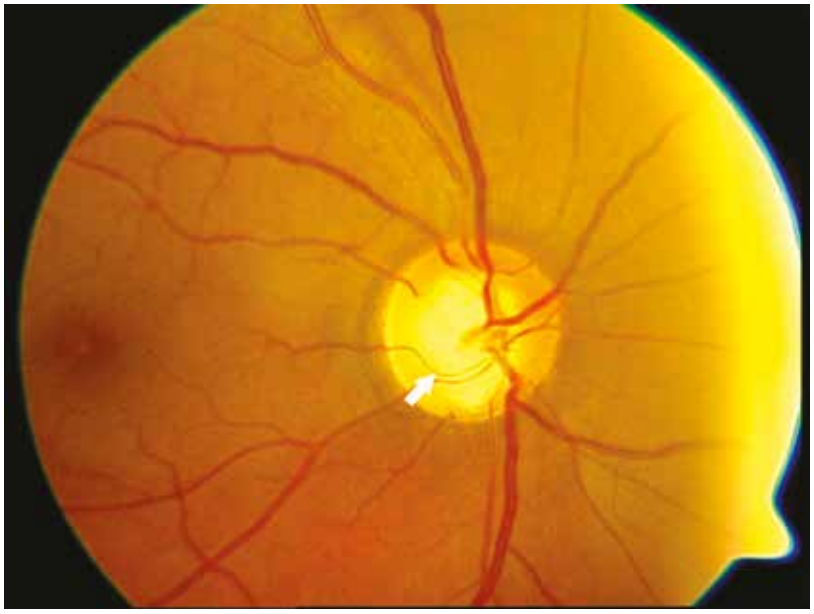

Figure 26: Baring of inferior circum-linear vessel (white arrow).

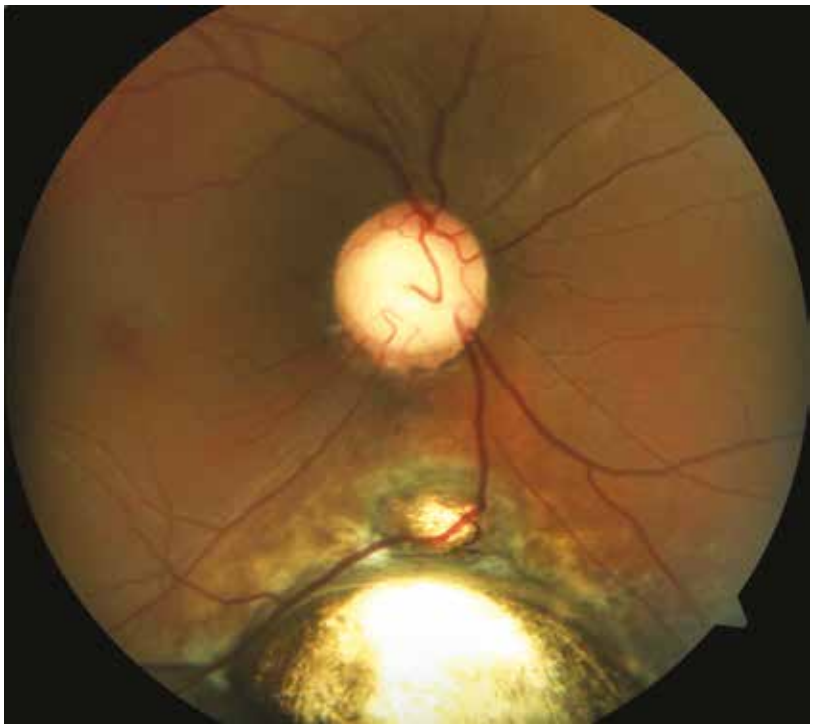

Figure 27: Optic disc coloboma with fundal coloboma appears as an inferior notch in optic nerve head.

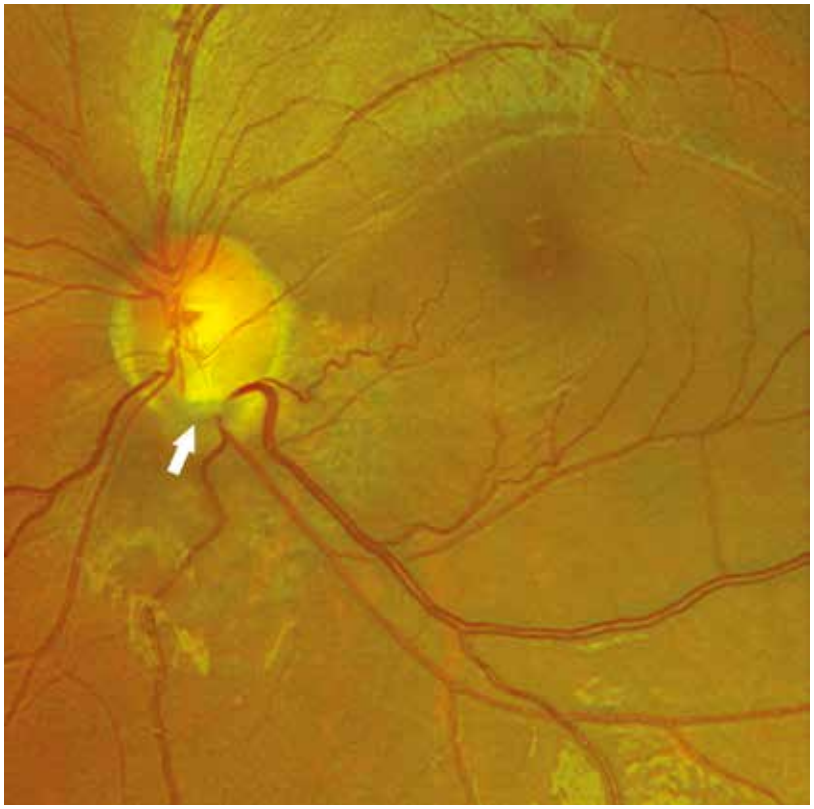

Figure 28: Optic disc pit (white arrow) appearing as inferior NRR thinning. (Picture courtesy: Dr. Divya Agarwal).

Optic Nerve Head Correlation with Visual Fields

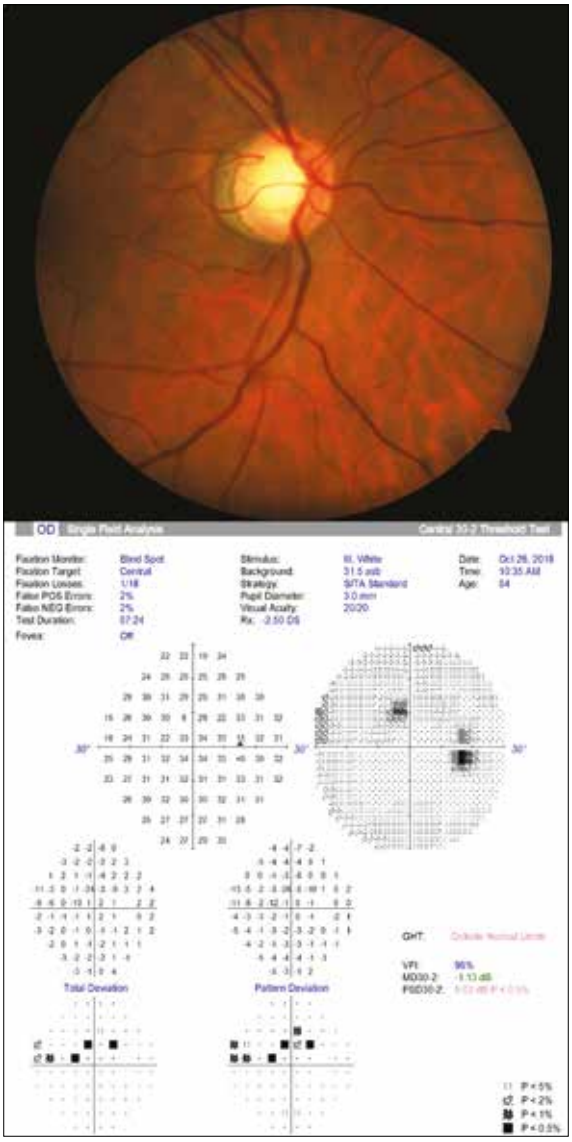

Figure 29: Early glaucoma with VCDR 0.8, NRR thinning and superior paracentral scotoma and nasal step on the visual field.

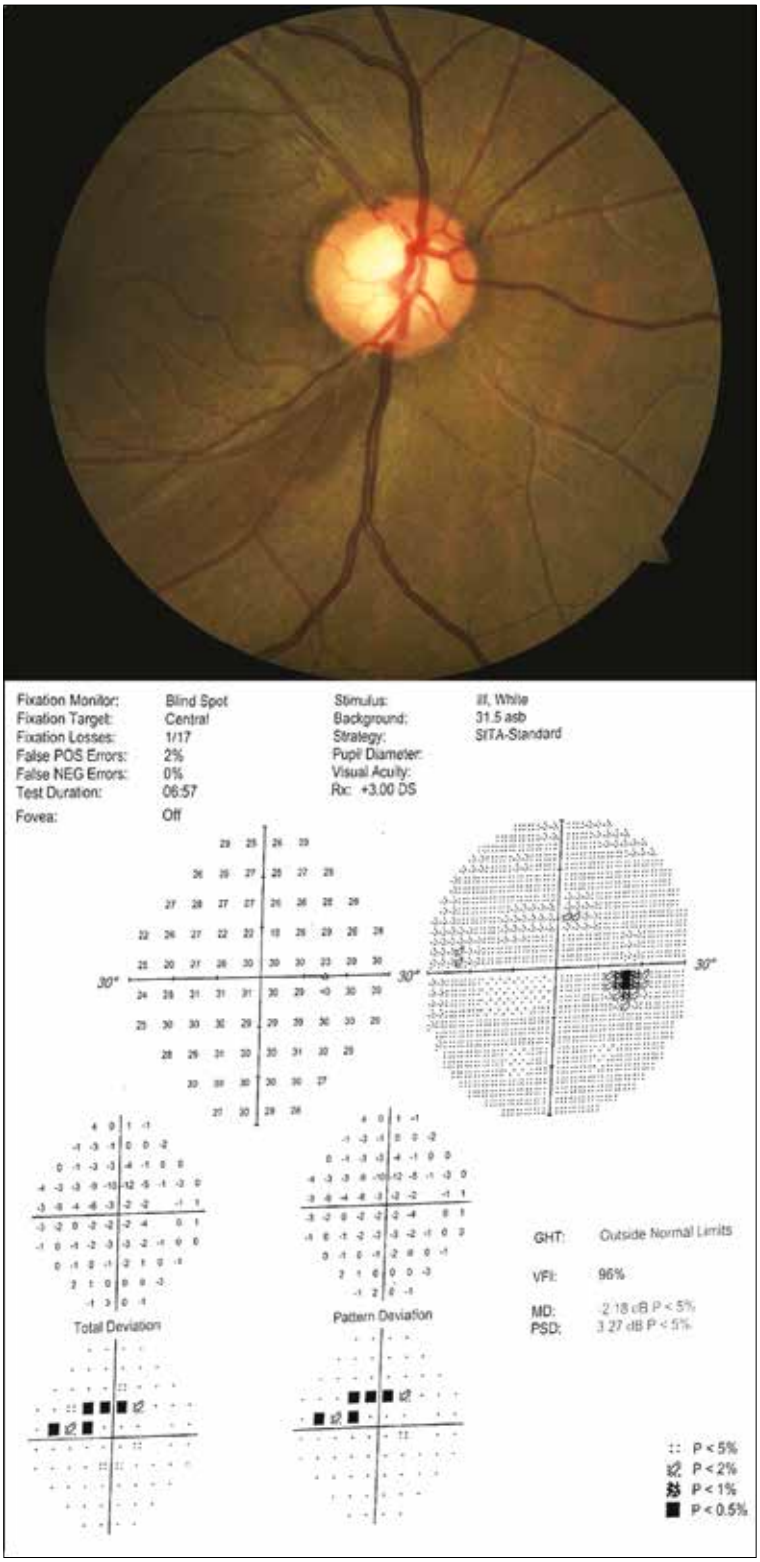

Figure 30: Early Glaucoma with inferior RNFL defect and a superior arcuate defect on the visual field.

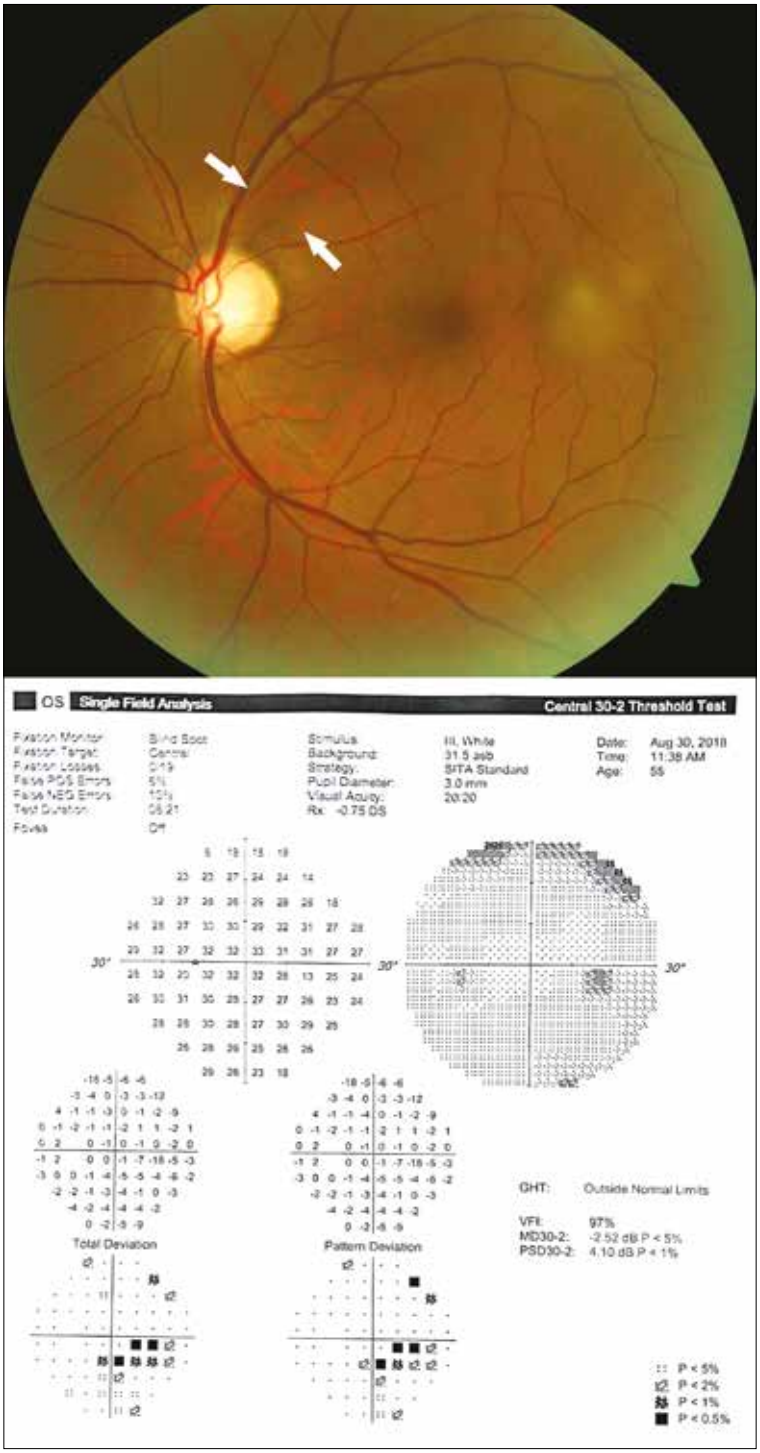

Figure 31: Early glaucoma with VCDR of 0.7, a superior RNFL defect (white arrows) and inferior paracentral scotoma on the visual field.

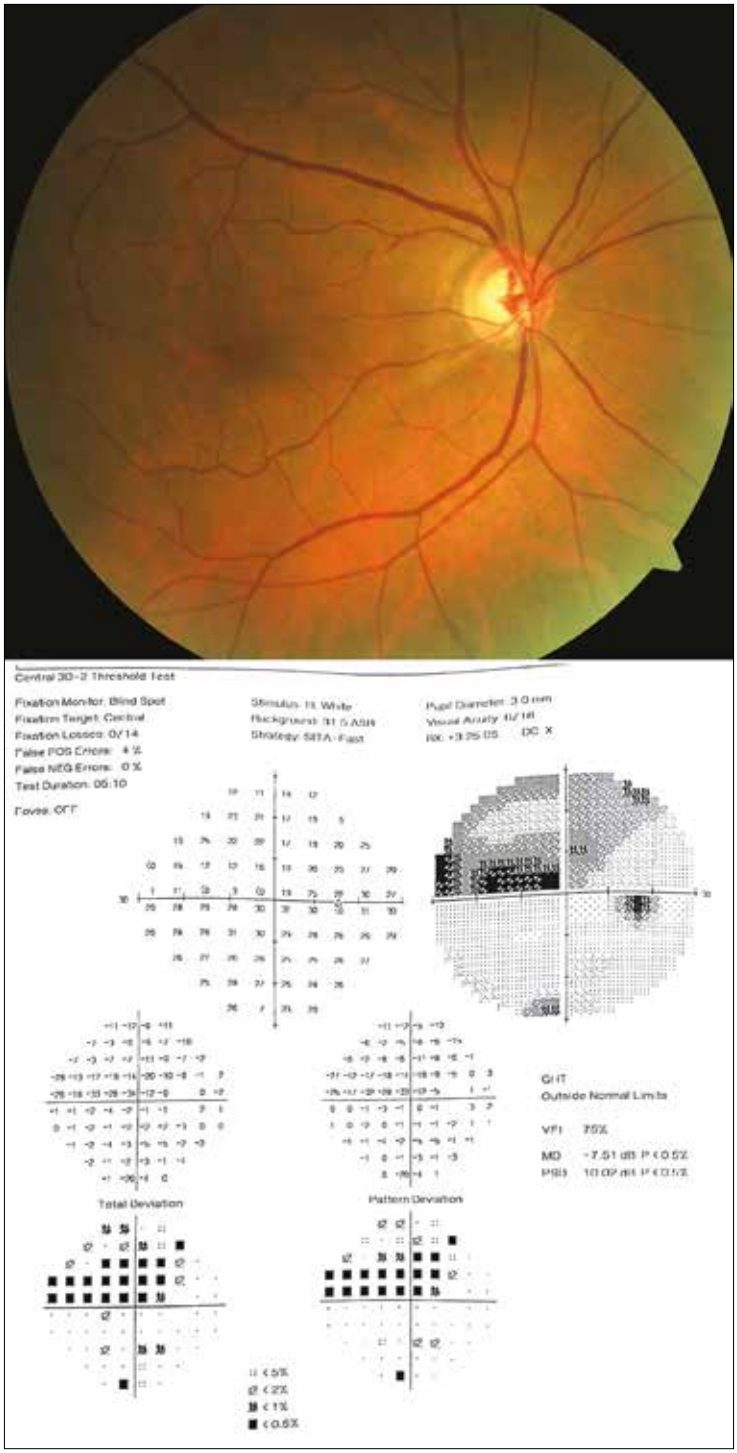

Figure 32: Moderate Glaucoma with VCDR of 0.7 and inferior notch, inferior RNFL defect and superior arcuate scotoma spreading outwards on the visual field.

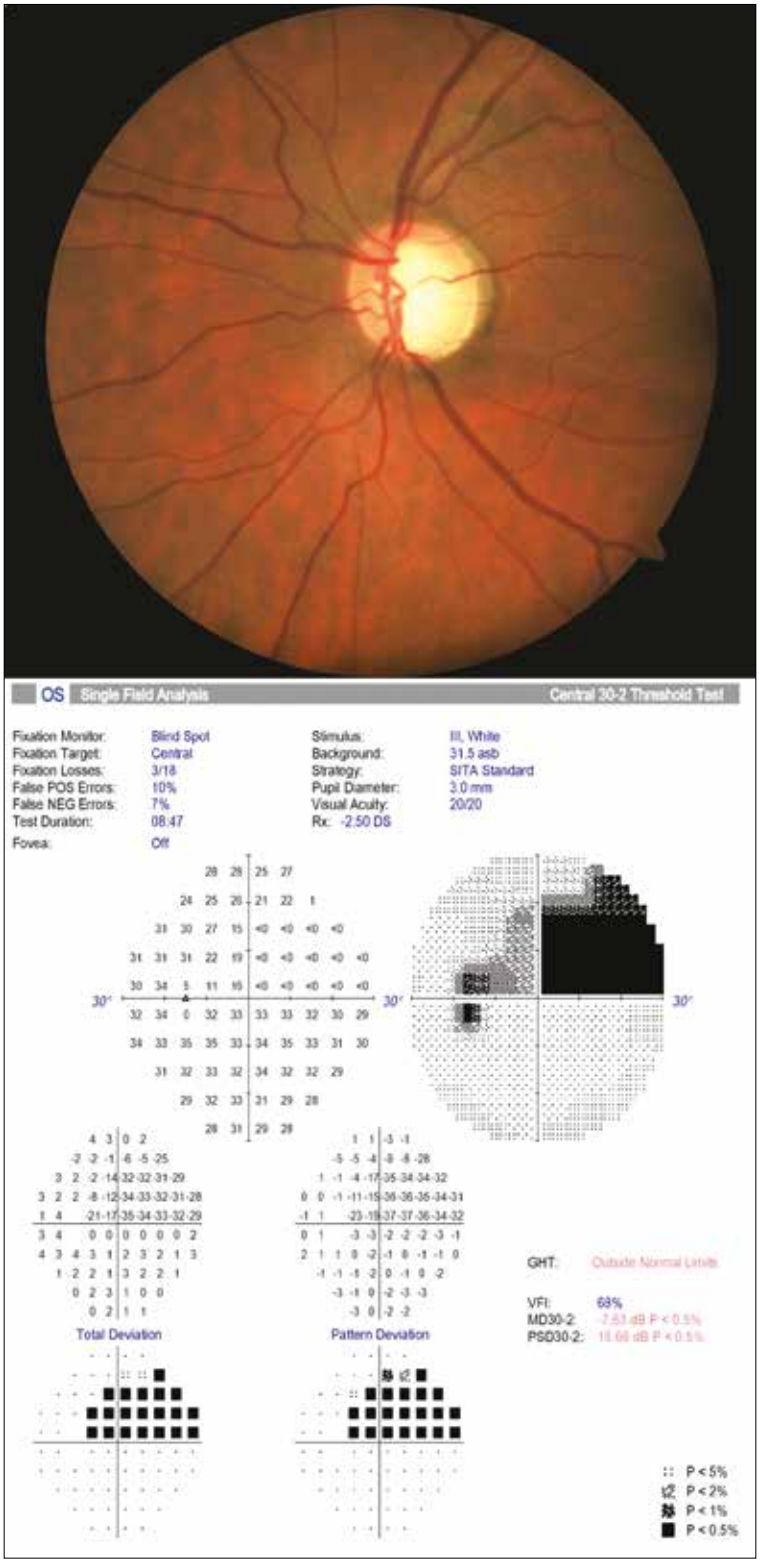

Figure 33: Moderate glaucoma with VCDR 0.8, inferior notch, RNFL defect and a superior arcuate scotoma covering almost entire superior hemifield.

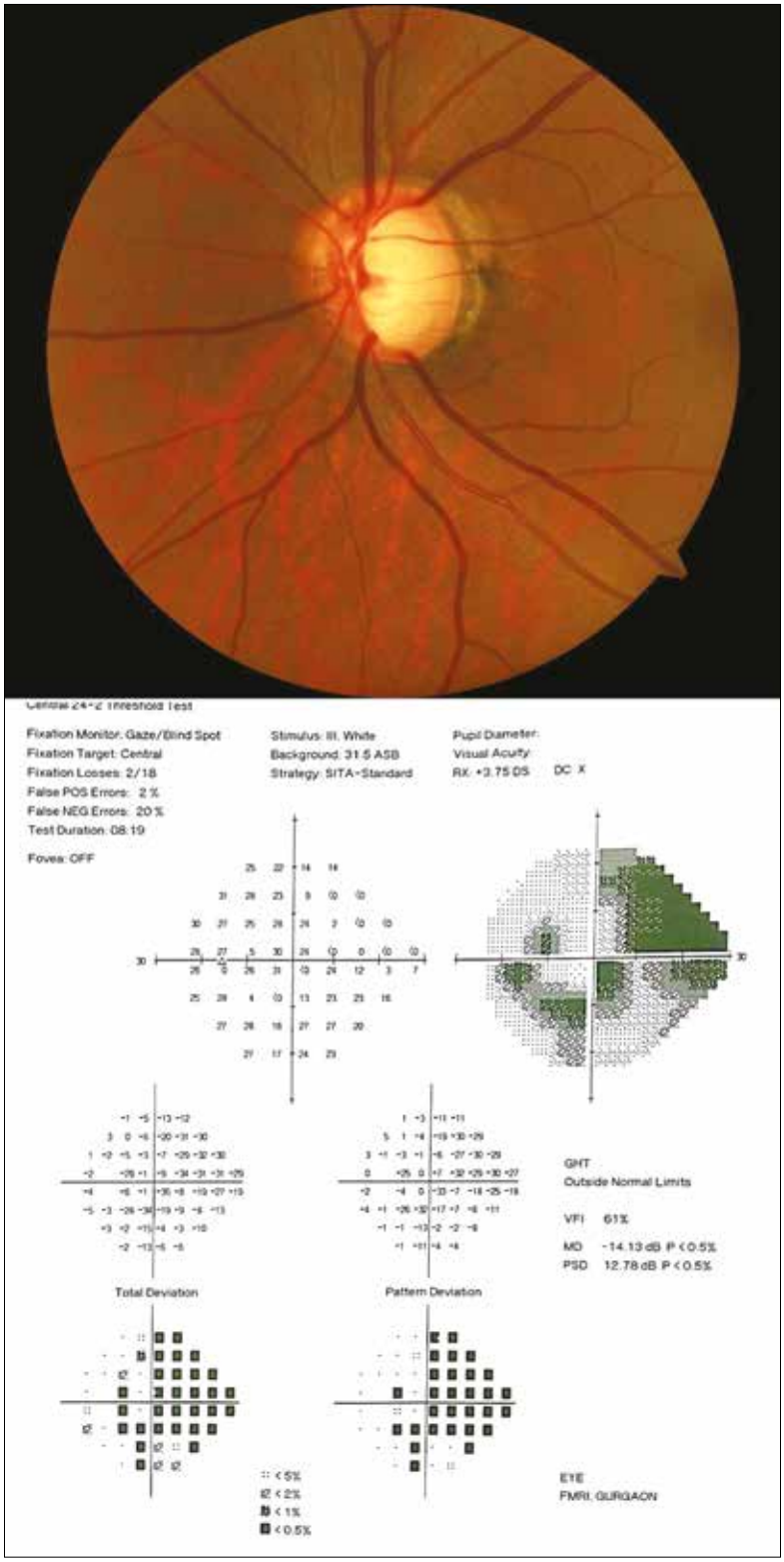

Figure 34: Advanced glaucoma with VCDR 0.9, severe NRR thinning and scotoma in both hemispheres on visual field.

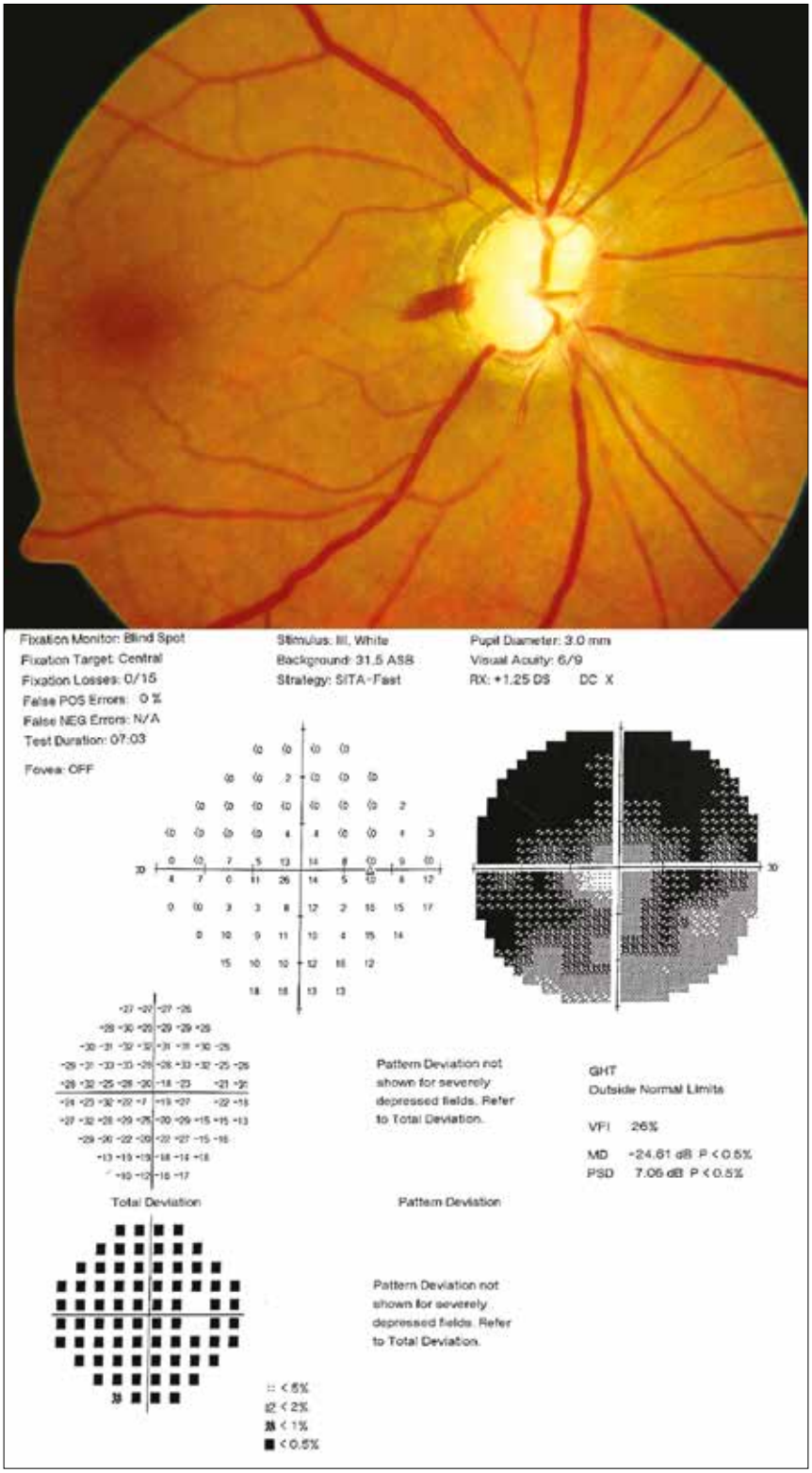

Figure 35: Advanced glaucoma with less than 10 degree central visual field remaining.

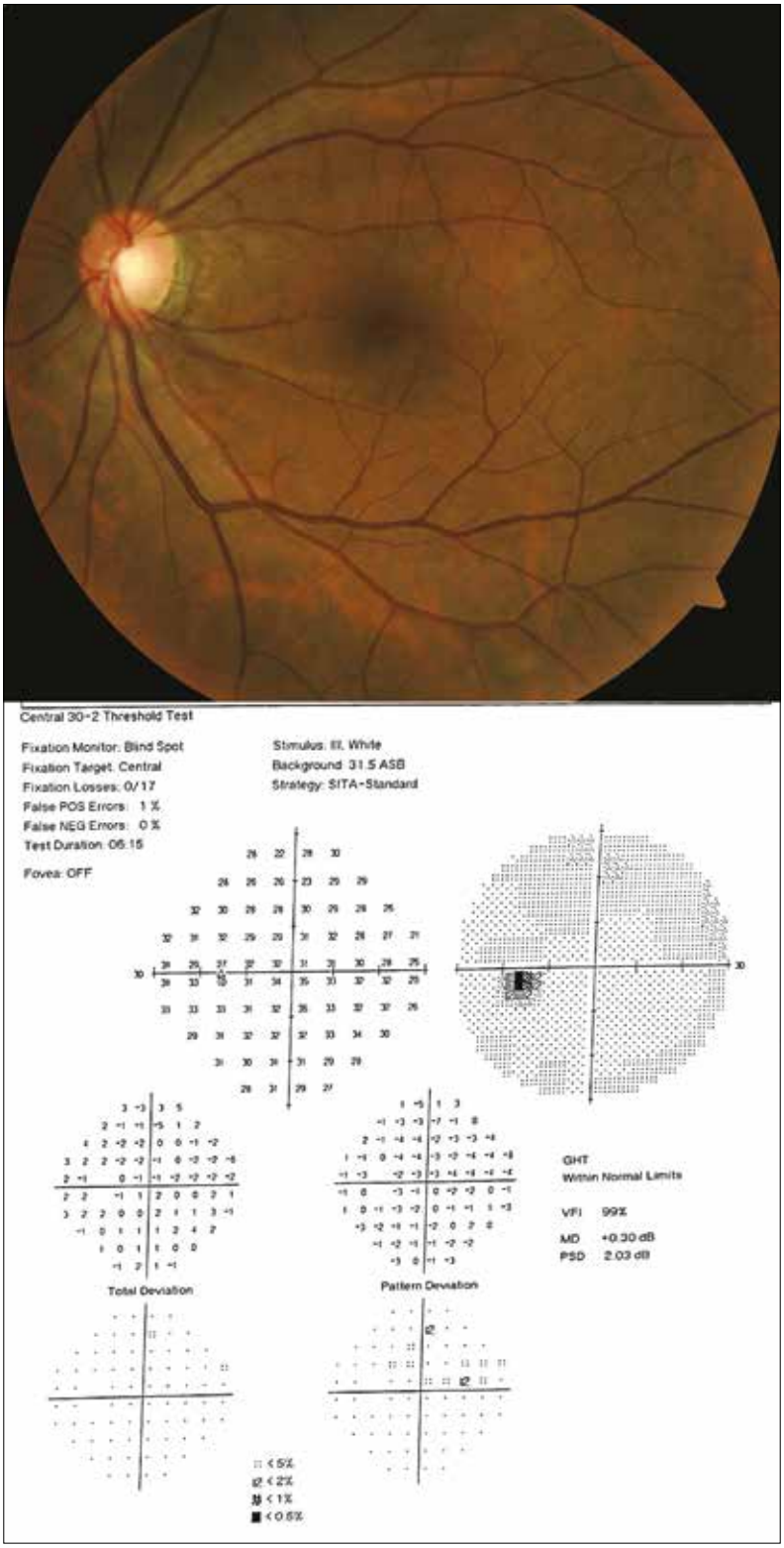

Figure 36: Inferior RNFL defect with normal visual field: Pre-perimetric glaucoma.

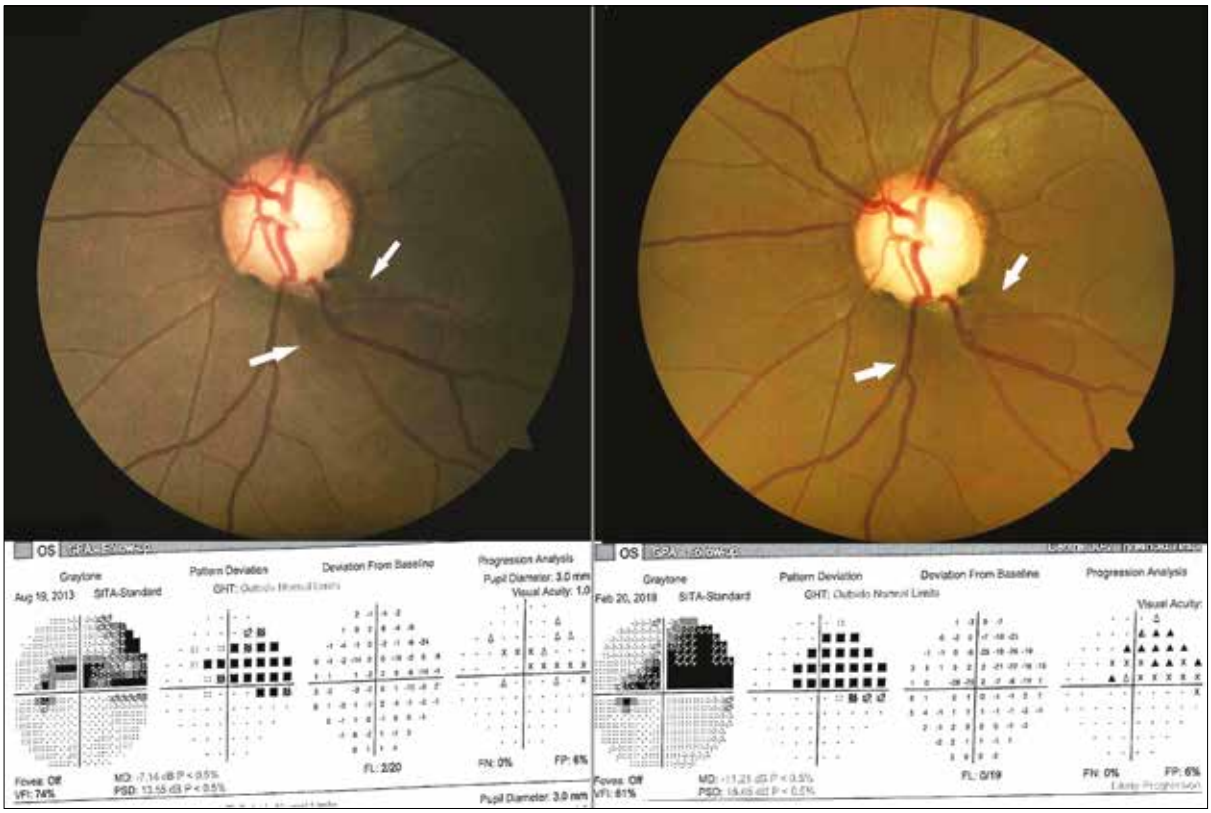

Figure 37: Progression seen on fundus picture as enlargement of RNFL defect (left image to right image); and corresponding change in visual field depression (see MD and PSD values).

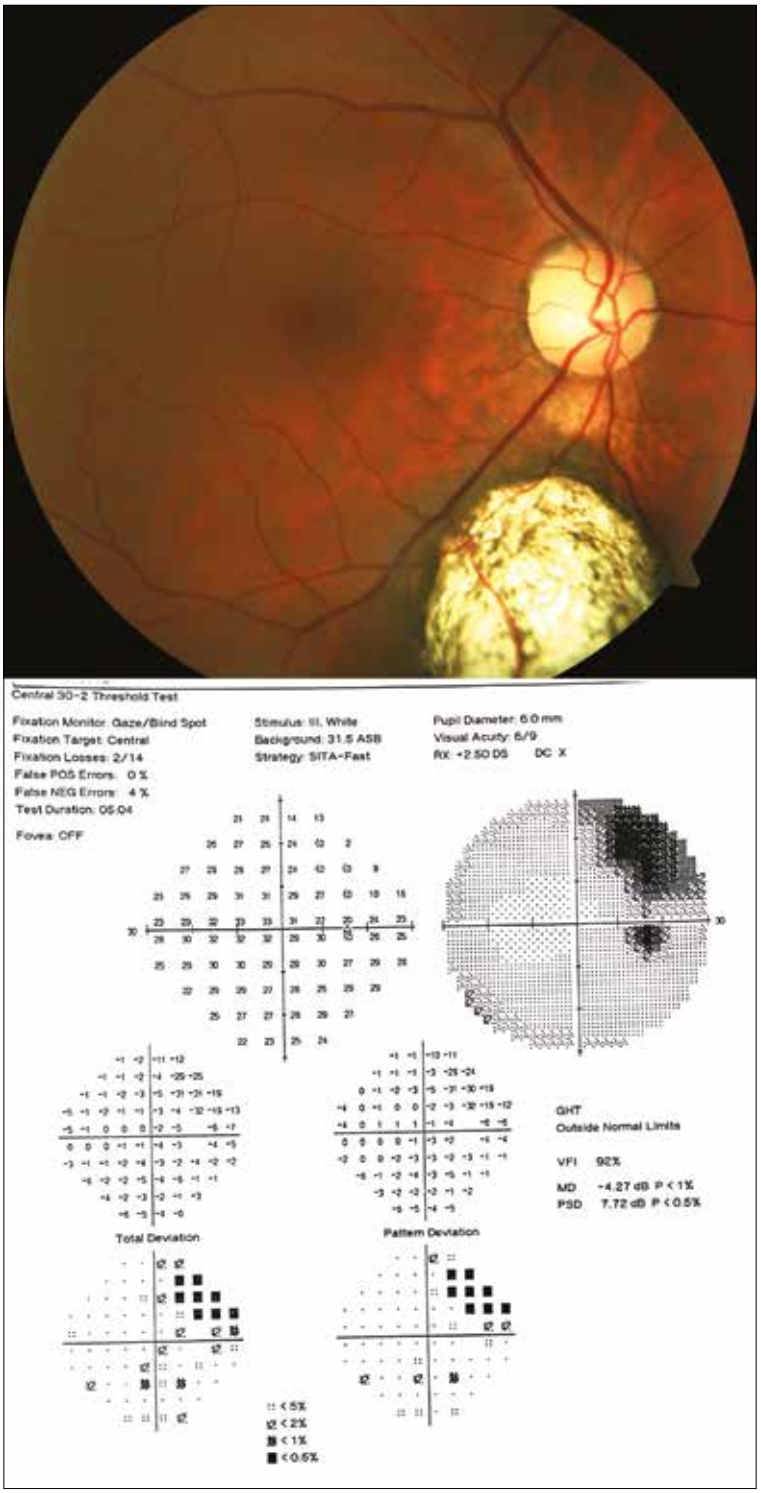

Figure 38: Isolated fundus coloboma may be confused as a glaucomatous field defect.

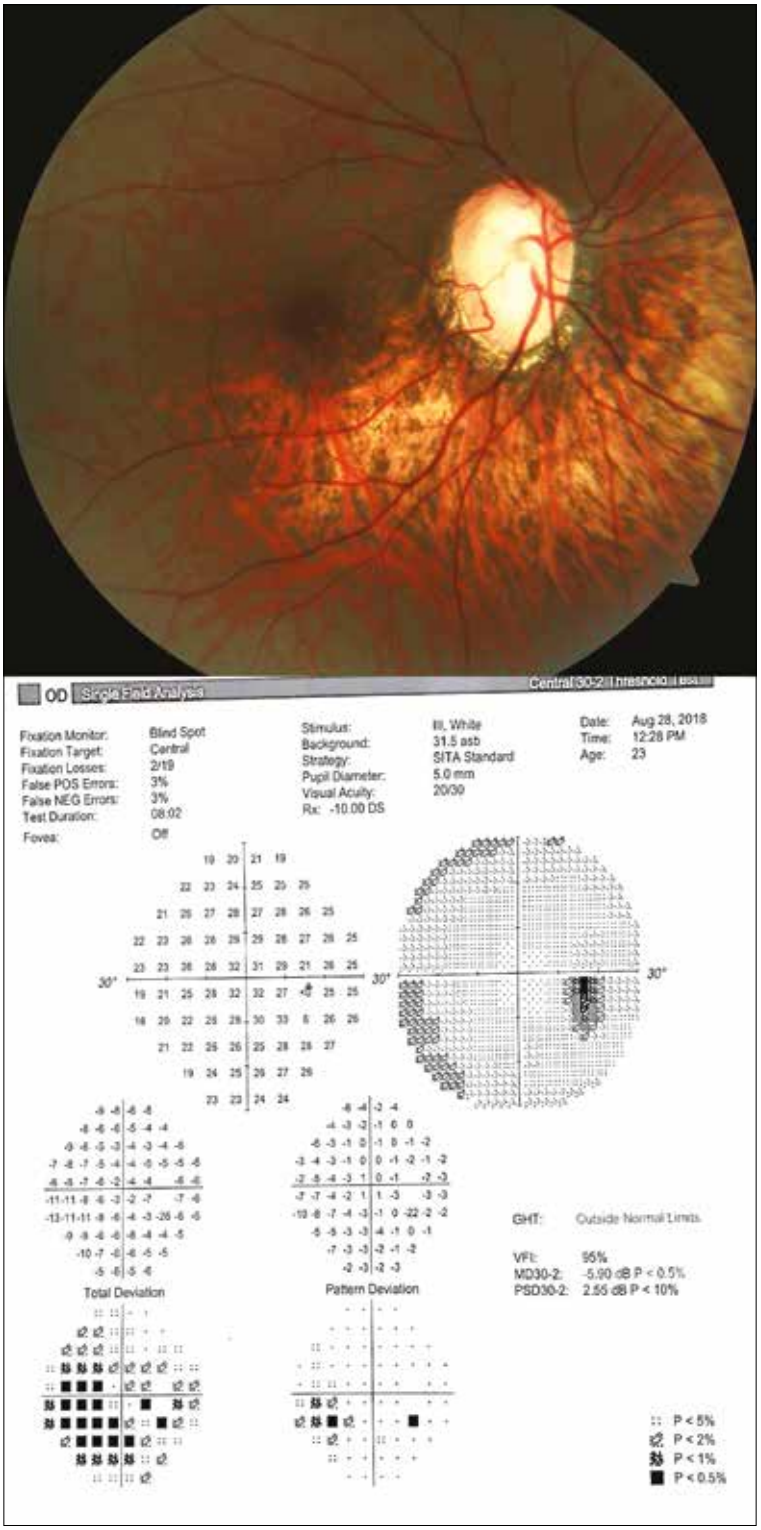

Figure 39: Disc dysplasia with high myopia leading to a false visual field defect.

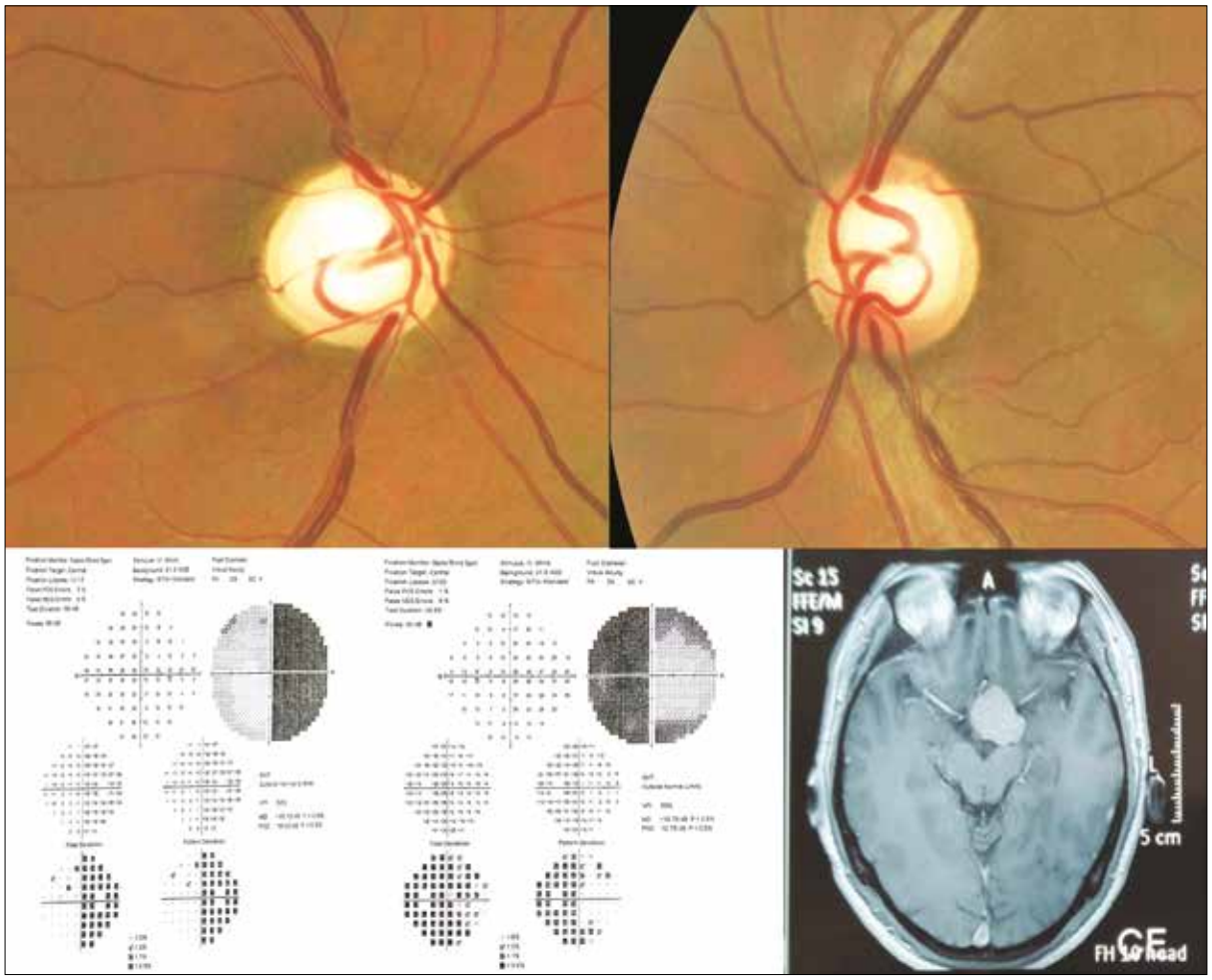

Figure 40: Concentric cupping with complete NRR pallor in right eye and bow-tie NRR pallor in left eye. Visual fields showed bitemporal hemianopia with a pituitary tumor on MRI.

Section - II

MEDICAL MANAGEMENT

Part - A

Principles of Therapy and Target IOP

Primary open angle glaucoma (POAG) is an intraocular pressure (IOP) sensitive, progressive, chronic optic neuropathy characterized by acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. Glaucoma therapy (medical, laser or surgical) is aimed at preventing further glaucomatous nerve damage.

The following important points need to be considered before you initiate therapy in a glaucoma patient:

- When you first see a suspected glaucoma patient, it is critical to rule out Primary Angle Closure Disease (PACD) as these patients need a peripheral laser iridotomy as the initial treatment (Refer to AIOS Guidelines on PACD).
- Dilate the patient and perform a detailed evaluation of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). Documentation of the optic disc with a photograph (red free and colour) is the best investigation if available and a drawing of the optic disc should be done with comment on the vertical cup-disc diameter ratio, any thinning of the NRR/loss of RNFL and disc hemorrhages.
- Never start therapy based on a single high IOP reading especially on non-contact tonometer (NCT). Always recheck the IOP with Goldmann Applanation Tonometer (GAT) and try and obtain 3 or 4 IOP values during the day before you start therapy, to ascertain highest baseline IOP. Ensure that the GAT or any other tonometer that you use is regularly calibrated.
- Record the Central Corneal Thickness (CCT) values and mention it along with the baseline IOP check. GAT is standardised for 520 µm and although there is no accurate formula for correlation of CCT and IOP, one should remember that high CCT values (> 570 µm) can lead to clinically significant over-estimation of IOP and low CCT values (< 470 µm) can lead to clinically significant under-estimation of IOP.
- The Target IOP for early glaucoma should it be ≤18 mmHg, for moderate glaucoma it hould be ≤15mmHg and for advanced glaucoma should be ≤12 mmHg. Target IOP is defined as the level of IOP at which progression of glaucomatous optic neuropathy can be halted. The target IOP basically depends on the severity of the disease (structural and functional optic

nerve damage) the and other factors that should be taken into consideration include speed of disease progression, the life expectancy, corneal thickness and hysteresis, family history, presence of Pseudoexfoliation (PXF)/disc haemorrhages and associated systemic disease.

- Patients with early glaucoma and medically well controlled IOP can follow-up 6 monthly for IOP check and 1 yearly for HVF and disc photos. Moderate to advanced disease should follow-up every 4 monthly for IOP check and 6 months to 1yearly for HVF. In case of suspected progression or uncontrolled IOP, closer follow-up at 2 monthly intervals or earlier is needed.
- Remember that you are treating the "patient" and not just the "IOP". Note down any physical/psychiatric diseases that the patient may be suffering from and make a list of all the drugs that the patient is taking as some of them may interact with the glaucoma medications or independently lead to elevation of IOP (esp. inhaled/oral/injectable/topical steroids). Psychological/emotional stress can also lead to an increase in IOP due to increase in endogenous cortisol.
- Discuss about the disease with the patient and his family and counsel them on the need for regular life long follow-up and treatment. Demonstrate the correct way to instill eye drops with occlusion of the puncta. Ask the patient to feed in an alarm/reminder into the mobile phone regarding the timing of the eye drops.
- Alleviate the anxiety of the family related to glaucoma blindness and discuss about positive lifestyle modifications such as regular aerobic exercises, deep breathing and meditation techniques for stress reduction both for the patient and the caregiver.
- A family history of glaucoma is the most important risk factor to be noted. All family members above the age of 40 should be called for regular screening.
- A careful anterior segment examination should be done to pick up any signs of Pseudoexfoliation and Pigment Dispersion. Pseudoexfoliation syndrome is characterized by severe disease and fast progression and requires a close follow-up. Patients with active Pigment Dispersion and concave iris configuration may benefit from a laser peripheral iridotomy (LPI) to decrease contact between the iris and zonules, although evidence for LPI is not very clear even with RCTs.
- Check the Blood Pressure of the patient and note it down. In patients with normal pressure glaucoma - low perfusion pressure due to low blood pressure may be an important cause for disease progression. Twenty-four hour Holter monitoring may be needed in a minority. Persons with normal pressure glaucoma with nocturnal hypotension or cardiovascular illness should be referred for proper titration of treatment. Beta blockers can reduce perfusion pressure and night dose should not be given in Normal Pressure Glaucoma / Low Tension Glaucoma.
- Any associated systemic disease such as Chronic Obstructive Pulmonary Disease (COPD), Non-Insulin Dependent Diabetes Mellitus (NIDDM), Coronary Artery Disease (CAD), Benign Prostatic Hypertrophy (BPH), Cerebrovascular disease (CVD), Arthritis, Depression, etc. and its treatment can have an adverse effect on glaucoma and must be referred to the appropriate specialist for treatment.
- It is very important to ascertain the financial condition of the patient and his/her ability to afford long term medical therapy.

- Some professions such as musicians playing high resistance wind instruments (eg. Trumpets), scuba divers, weight lifters, etc. may be associated with prolonged periods of elevated IOP.
- If the patient has moderate-advanced glaucoma with significant visual field defects (esp. inferior hemifield), he should be counselled against driving due to an increased risk of motor vehicle accidents.
- If you prescribe any eye drop to the patient, discuss the common side effects expected after putting the drug and symptoms of ocular allergy.
- Always check for pregnancy and lactation before prescribing eye drops in Juvenile Glaucoma patients.
- In patients with ocular surface disease, preservative-free or atleast Benzalkonium Chloride (BAC)-free drugs would be preferred.
- Laser trabeculoplasty can be performed at any stage of the disease to reduce IOP but it is more effective as initial therapy in ocular hypertension or early glaucoma. The effect wears off over time and the patient needs to be counselled to come for repeated follow-up as medications may be required to control IOP.
- Micropulse laser therapy should not be used as primary therapy to lower IOP in POAG patients with visual potential as the results are unpredictable, it has risk of prolonged inflammation and sight threatening complications have been reported. However, it can be used to lower IOP in POAG patients who are uncontrolled on maximum tolerable medical therapy, are non-compliant or in those with failed trabeculectomy surgery. However, the risk of complications such as prolonged inflammation, cystoid macular edema, and other sight threatening complications should be discussed.

Goals of Glaucoma Therapy

Glaucoma therapy should be able to maintain the health-related quality of life of the patient. The basic goals of glaucoma therapy are the following:

- To achieve target IOP and dampen IOP fluctuations with minimal possible medications.
- To administer glaucoma medication which have the least side effects on the quality of life of the patient.
- To achieve the treatment goal at an affordable and sustainable cost for the patient.
- Monitor the structure and function of the optic nerve for disease progression and adjust the target IOP to a lower level if disease progression occurs.
- To treat non-IOP dependant systemic factors (NIDDM, CVD, systemic hypertension, low diastolic perfusion pressures, hyperlipidemia, vasospasm, CAD) which may contribute to the development and worsening of the disease.
- To educate and involve the patient and his family in the management of the disease process.

How to start treatment?

Once the diagnosis of glaucoma has been made, ocular hypotensive medications are started to lower IOP.

Monocular therapeutic trial

In eyes with Ocular Hypertension (OHT) and early POAG or unilateral damage where the patient can come for regular follow-up, a monocular drug trial is ideal as it helps to determine the efficacy as well as safety of the glaucoma medication. Therapy is started in the worse eye (usually with higher IOP/more structural and functional damage) first and IOP checked at 3 or 4 time points after 4-6 weeks.

If the drug achieves the target IOP, it is continued and started in the second eye. If drug fails to reduce IOP by at least 20% IOP from baseline or produces severe side effects, the drug is withdrawn; and unilateral drug trial with the second option is done.

In eyes with moderate-severe disease or bilaterally high IOP or in situations where the patient is unable to return within 4-6 weeks to assess the results of the monocular trial, treatment can be started in both eyes

When to Switch or Add Therapy?

A. **Switch:** If a drug fails to reduce IOP by atleast 20% from baseline or produces severe side effects, we switch to another class of drugs.

When to switch outside class?

Usually, patients are switched outside class if switch is made for attaining the desired IOP reduction.

When to switch within class?

Switching within class may be done to minimise local adverse reactions or in non-responders to Prostaglandin analogues.

- **Alpha agonists:** It is believed that the allergic reaction associated with brimonidine (0.2%) may be caused by the immunologically active drug-protein haptens instead of the preservatives. Therefore, a patient known to be allergic to brimonidine with BAC should discontinue the medication instead of switching to brimonidine with purite (0.15%; 0.1%) or vice versa.
- **Beta blockers:** Patients on beta blockers who show an allergic response to BAC may benefit from switching to preservative-free timolol or gel-forming formulations of timolol, which uses benzododecinium bromide as preservative.
- **Carbonic anhydrase inhibitors (CAIs):** Complaints of ocular hyperemia and watering are generally associated more with dorzolamide use and foreign-body sensation and blurred vision are more likely with brinzolamide use. Less hyperemia and watering associated with brinzolamide may be secondary to the more neutral pH than dorzolamide, and the higher rate of blurred vision may be due to the suspension

formulation of brinzolamide. Hence, switching between these two agents may be based on tolerability.

B. **Add/Combine:** If the first drug reduces the IOP more than 20% from baseline but if the target IOP level is not reached, a second drug is added.

Combining drugs:

- When adding the second drug, consider its safety, efficacy, frequency of dosing, cost, and the additive effect that it can offer to the medication already in use. Drugs with different mechanism of action are best combined (eg. Drug A decreases inflow and Drug B increases outflow)
- A time interval of at least 5 minutes should be given before administering the second drop.
- Medications should be added one at a time if possible to avoid confusion regarding efficacy and tolerability.
- In case IOP does not reach target IOP with three to four topical anti-glaucoma medications, laser/filtering surgery should be considered.
- **Maximal Therapy** - Combination therapy can be given with prostaglandin-beta blocker once in the morning and CAI-alpha agonist twice daily.
  Using combination eye drops with two drugs in the same bottle is a good choice if more than one drug is required as it decreases the number of eye drops to be instilled into the eye, decreases the cost of therapy, decreases preservative induced conjunctival toxicity and increases compliance.

Pregnant and lactating patients

Some basic rules to remember for pregnant or lactating glaucoma patients:

- Avoid the use of ocular hypotensive medications during the first trimester. Prostaglandins have a theoretical risk of spontaneous abortion or pre-term labour and should be avoided until 36 weeks of pregnancy. They can be used safely after this time, and during breast feeding.
- If medication is necessary, brimonidine is the safest choice followed by timolol gel-forming solution and carbonic anhydrase inhibitors. Brimonidine (or alpha agonists) causes respiratory depression in premature infants, and should be stopped upon delivery.
- Use punctal occlusion/digital occlusion of tear duct to minimize systemic absorption.
- Consider Selective laser trabeculoplasty (SLT) or filtering surgery without antimetabolites in high-risk cases. The second trimester is the optimal time for surgery.
- During breastfeeding, beta blockers/CAIs are acceptable, but dosing should be done immediately after nursing to minimize the concentration in breast milk.

How to instill the eye drops?

The patient is instructed to wash his/her hands prior to instillation. With head tilted slightly backwards while gazing upwards, the lower lid is gently pulled down with the non-dominant hand to form the forniceal concavity. With the dominant hand, the drop dispenser is positioned just over this forniceal pouch. The bottle should be near enough to make sure the drop falls in the eye and far enough to avoid touching the lid margin. After instillation, eyes should be kept closed and digital compression should be applied over the punctum for 1-2 minutes to minimize systemic absorption. Any excess drops should be immediately wiped with a tissue.

PART - B

Ocular Hypotensive Medications

Introduction

The ideal medication is one that is effective in lowering IOP, has minimal side effects, is cost effective, and is easy to comply with. There is no ideal glaucoma drug at present.
One must choose wisely between the first-choice agent and the first-line agent for each patient, so that patient can remain compliant to the life long therapy.

- "First-choice agent" is the drug chosen on medical grounds.
- "First-line agent" is selected on non-medical (usually cost) grounds.

There are five classes of topical hypotensive medications: hypotensive lipids, beta blockers, selective (alpha-2) adrenergic agonists, carbonic anhydrase inhibitors (CAIs), and cholinergic agents.

a. Hypotensive lipids:

All drugs in this category are derivatives of prostaglandin F2 alpha, and can be divided into three sub-categories:

- Prostaglandin analogues (PGAs): Latanoprost (0.005%), Travoprost (0.004%) and Tafluprost (0.0015%)
- Prostamide: Bimatoprost (0.03% and 0.01%)
- Deconsanoids: Unoprostone isopropyl (0.15%).

The most commonly used PGAs in clinical practice are latanoprost, bimatoprost and travoprost.

Mechanism of action:

These drugs have a dual mechanism of action; increase both trabecular meshwork and uveoscleral outflow. They cause extracellular matrix remodeling between the longitudinal ciliary muscle fiber bundles, alteration in matrix metalloproteinase secretion, and opening of flow pathways, increasing uveoscleral outflow over time. The action of each drug is mediated through different prostaglandin receptors and hence in cases where one drug is not effective, another PG analogue can be tried.

Indications:

- POAG including normal tension glaucoma
- Secondary open angle glaucoma (pseudoexfoliation syndrome, pigment dispersion syndrome)
- Primary angle closure glaucoma (PACG): Increase the uveoscleral outflow by gaining access to the ciliary body either through the partially open part of the anterior chamber angle or through other routes such as the posterior chamber between the iris and lens, the iris root itself, or the sclera.
- Limited efficacy in paediatric glaucomas.

Contraindications:

Absolute contraindications: None

Relative contraindications:

- Recent intraocular surgery; especially in eyes operated for cataract with intraoperative complications such as posterior capsular rent
- History of herpetic keratitis
- Active uveitis: Some studies have shown the effectiveness and safety of PGAs in uveitic glaucoma.
- Unilateral glaucoma
- Pregnant women
- Diabetic macular edema

Efficacy and dosage:

- IOP reduction ranging between 25 to 35%, after 1 week of once daily bedtime instillation. Unoprostone is the only drug which is dosed twice daily.
- Reduction in IOP starts 2-4 hours after instillation. Maximum therapeutic effect 8-12 hours after instillation.
- Minimizes IOP fluctuations over 24 hours.
- Maximum IOP lowering 3-5 weeks after initiation of therapy. Follow-up the patient 3 weeks after starting these drugs, to ascertain IOP lowering response.
- Contact lenses should be removed prior to instillation of the drug and may be reinserted after 15 minutes.
- Non-responder rate is approximately 10%

Adverse Effects:

- Conjunctival hyperemia
- Burning and Itching
- Iris color changes
- Hypertrichosis (Figure 1)

- Periorbital skin hyperpigmentation
- Prostaglandin associated periorbitopathy: Periorbital fat loss, dermatochalasis, and deepening of the upper eyelid sulcus

Figure 1: Elongation of eyelashes after prolonged use of PGAs.

b. Beta adrenergic blockers:

Depending on their selective receptor inhibition, beta blockers are classified as:

- **Non-selective:** Timolol maleate, levobunolol, nadolol, befunolol, carteolol, penbutolol, labetalol, nipradilol are nonselective β -blockers.
- **Selective:** Betaxolol, atenolol and metoprolol are selective β1-blockers

Commonly used topical beta blockers for ophthalmic use are: timolol (maleate and hemihydrate), betaxolol and levobunolol.

Mechanism of action:

Beta blockers antagonize β-1 and β-2 receptors in the ciliary body's non-pigmented epithelium and thereby reduce secretion of aqueous humor through direct action on the ciliary body, which in turn lowers IOP. The other mechanisms proposed are direct vasoconstriction of the ciliary vessels, calcium channel blocking action and blockage of serotonin receptors.

Indications:

- All forms of glaucoma.
- Beta-blockers are additive in combination with miotics, adrenergic agonists, both topical and systemic CAIs and PGAs.

Contraindications:

- Avoid in smokers and in those with a history of bronchospastic disorders.
- In diabetics, as beta blockers may mask the symptoms of hypoglycemia.
- In patients with heart disease, bradycardia, arrhythmia, heart block, or cardiac failure.
- Caution in pregnant women and nursing mothers as it may cause fetal bradycardia and arrhythmia.

- Topical beta blockers may not be fully effective in patients already on systemic beta blockers.
- They should be used carefully in drugs that decrease the heart rate like anti-arrhythmic drugs.

Efficacy and dosage:

- Non-selective beta blockers lower IOP by 20–30%.
- One drop of timolol maleate 0.25% or 0.50% has its peak effect 2 hrs following administration and may last for 24 hrs. Can be given twice-a-day or once in the morning (gel formulations).
- Maximum effect is seen 2 weeks after starting therapy.
- Residual effect of timolol on IOP may be detected for as long as 2–3 weeks, and beta blockade can be detected up to 1 month after discontinuation of the drug due to melanin binding, the "depot storage" effect.
- Timolol has little effect during sleep because the nocturnal aqueous secretion is less than half of what is seen during daytime hours.
- Non-responder rate is approximately 20%.
- Less effective in patients already taking oral beta blockers.
- **Short Term Escape:**
  - Seen in up to 20% of cases.
  - Loss of initial IOP reduction within 2–3 weeks.
  - May be due to an upregulation in the number of ocular beta receptors after initial complete blockade.
- **Long-term drift:**
  - Loss of IOP control after many years of therapy, or even within 3 months.
  - May be the result of drug tolerance or progression of the trabecular meshwork outflow problems.

Adverse effects: Both local and systemic adverse effects are known.

a) Ocular

- Burning/pain/discomfort
- Hyperemia of conjunctiva
- Superficial punctate keratitis
- Corneal anesthesia
- Allergic blepharoconjunctivitis
- Dry eye
- Hypotony

b) Systemic

- Depression
- Anxiety
- Confusion/Disorientation /Hallucinations
- Fatigue/Weakness/Drowsiness
- Exacerbates myasthenia gravis

- Tinnitus
- Abnormal taste sensation
- Emotional lability
- Cerebrovascular accident
- Psychosis
- Bradycardia
- Raynaud's phenomenon
- Arrhythmia
- Heart failure
- Hypotension
- Hypertension
- Syncope
- Myocardial infarction
- Dyspnea
- Status asthmaticus
- Pulmonary failure
- Apnea, especially in children
- Maculopapular rash
- Alopecia
- Urticaria
- Abdominal cramping
- Impotence
- Altered response to hypoglycemia

Should Beta Blockers Still Be Used as a First-Line Agent?

Prior to Prostaglandin analogs, timolol was the drug of choice for all forms of glaucoma. Although timolol and other beta blockers are not as potent as prostaglandin analogues, they can still be used as a first-line agent. This class of medication remains efficacious, well-tolerated, and cost effective.

c. Alpha adrenergic agonists:

Two topical alpha-adrenergic agonists are available for glaucoma therapy:

- Apraclonidine: Relatively non-selective for alpha 1 and alpha 2 receptors. Not available in India.
- Brimonidine: More selective for alpha 2 than alpha 1 receptors. Brimonidine is 23 times more alpha 2 selective than apraclonidine and 12 times more selective than clonidine.

Mechanism of action:

These drugs act by preventing the release of norepinephrine at presynaptic terminals. They decrease aqueous production, and may have some effect on episcleral venous pressure as well as uveoscleral outflow. Brimonidine may also affect conventional outflow in a positive manner. Brimonidine increases blood flow of the optic nerve head and may have some neuroprotective effect.

Indications:

- For acute prophylaxis of IOP elevation following Nd:YAG and argon laser iridotomy, argon laser trabeculoplasty, Nd:YAG capsulotomy, and cataract surgery.
- Mostly used as an adjunctive agent for most forms of glaucoma.

Contraindications:

- Patients taking monoamine oxidase inhibitors (MAOIs) because they may precipitate a hypertensive crisis.
- Patients taking tricyclic anti-depressants because of an increased risk of central nervous system mediated depression.
- Brimonidine has been associated with respiratory and cardiac depression in infants and is contraindicated under the age of 2 or body weight less than 15 kg.
- Caution is required in treating patients with:
  - Unstable and uncontrolled cardiovascular disease.
  - Cerebral or coronary insufficiency
  - Raynaud's phenomenon
  - Orthostatic hypotension
  - Thromboangitis obliterans

Efficacy and dosage:

- IOP lowering efficacy is between 20% and 25%.
- Dosed three times a day in monotherapy, and twice-a-day in fixed-dose combinations.
- Little effect on nocturnal IOP.

Adverse effects: The most frequent side effects reported with brimonidine are dry mouth, conjunctival hyperemia, systemic hypotension, fatigue, and drowsiness, especially in children. It also leads to allergic blepharoconjunctivitis (Figure 2) and follicular conjunctivitis.

Brimonidine may cause fatigue and/or drowsiness which may impair the ability to drive or to use machinery; additionally some patients report blurry vision after instillation; hence should not be prescribed to people working with heavy machinery.

The brimonidine-purite formulations are preferred to brimonidine-benzalkonium chloride (BAC) formulations due to better tolerability while maintaining similar efficacy.

Figure 2: Allergic Blepharo-conjunctivitis due to brimonidine use.

d. Carbonic anhydrase inhibitors (CAIs):

- **Systemic CAIs:** Acetazolamide (most commonly used), Methazolamide and dichlorphenamide
- **Topical CAIs:** Dorzolamide and Brinzolamide

Mechanism of action: These drugs inhibit the enzyme carbonic anhydrase in the ciliary epithelium which inturn reduces aqueous production. Both systemic and topical CAIs cause IOP reduction by a reduction in the accumulation of bicarbonate in the posterior chamber, with a decrease in sodium and associated fluid movement linked to the bicarbonate ion. High doses of acetazolamide bring about an additional decrease in IOP by relative metabolic acidosis.

Indications:

- Systemic CAIs are used where pressure reduction is needed on an immediate basis.
- Topical CAIs serve as reasonable first (especially in very young or very elderly) or second choice therapy for all forms of glaucoma.

Contraindications:

- Patients with sulfonamide allergy (sulfa cross-reactivity)
- Patients with a history of kidney stones or other renal disease, patients with creatinine clearance <30ml/min.
- Patients with liver disease
- Patients with cardiac disease
- Patients with Addison's disease
- Patients with severe chronic obstructive pulmonary disease

Efficacy and dosage:

- Effect is seen by 30 minutes, reaches maximum effect by 2 hours and lasts for 6 to 8 hours. The washout period is 3 days.
- Topical CAIs lower IOP by about 20% and the oral CAIs by approximately 30%.
- Acetazolamide is the most commonly used, and is available as 250-mg tablets, or sustained-release capsules. It can be dosed upto 1g/day in four divided doses for immediate release

tablets and two divided doses for sustained release capsules.

- Suggested frequency of instillation for dorzolamide 2% and brinzolamide 1% is three times daily in monotherapy and twice daily in fixed dose combination with timolol.
- Patients on an adequate oral CAI dose are unlikely to have an additional advantage of a topical CAI.
- Topical CAI may supplement the IOP reducing effect when patients are on less than a full therapeutic dose of oral CAI.

Adverse effects:

Oral CAIs:

- Malaise, fatigue, paresthesia, weight loss, depression, gastrointestinal distress, and nephrolithiasis.
- Cannot be given for long-term due to risk of blood dyscrasias, hearing loss, metabolic acidosis and electrolyte imbalance, mainly hypokalemia and hence long term oral CAIs should be given along with potassium supplementation.
- Choroidal detachment and transient myopia are rare side effects.

Topical CAIs:

- Stinging, discomfort, bitter taste and allergic conjunctivitis are common adverse effects with chronic use of topical CAIs.
- Patients with compromised endothelial function, may develop superficial punctuate keratitis, corneal edema, reversible or irreversible corneal decompensation due to inhibition of Na^+/K^+ ATPase and the bicarbonate dependent Mg-ATPase which use CA-II and CA-IV.
- Ocular surface irritation with dorzolamide may be a result of the drug's relative greater acidity (lower pH) when compared with that of brinzolamide.
- Brinzolamide suspension may cause more blurring than the dorzolamide solution.

e. Cholinergics (Miotics; Parasympathomimetic agents):

The parasympathomimetics effectively lower lOP but are often poorly tolerated because of ocular side effects.
The miotics are subdivided into two classes based on mechanism of action:

- **Direct acting (Cholinergic agents):** Pilocarpine and Carbachol
- **Indirect acting (Cholinesterase inhibitors):** Echothiophate iodide.

These days the only ocular cholinergic agent used for therapeutic purpose world over is pilocarpine.

Mechanism of action:

Pilocarpine lowers the intraocular pressure by contracting the sphincter pupillae and the ciliary body muscles that are connected to the scleral spur to open the trabecular meshwork mechanically thereby increasing the outflow of aqueous humor through the conventional drainage pathways.

Indications:

- Pilocarpine 1% to 2% is used for the acute treatment of primary angle closure glaucoma (PACG). It is most effective once the IOP has been reduced by aqueous suppressants and hyperosmotic agents and the blood flow to the ischemic iris has been restored.
- Pilocarpine 1-2% eye-drops can be used in patients with primary angle closure (PAC), PACG and combined mechanism glaucoma for additional IOP reduction.

Contraindications:

- These agents are contraindicated in patients aged over 40 years, with cataract, uveitis, phacomorphic glaucoma, and neovascular glaucoma.
- Other contraindications include uncontrolled asthma, spastic gastrointestinal disturbances, peptic ulcer, bradycardia, hypotension, recent myocardial infarction, epilepsy, parkinsonism, Alzheimer's disease and retinal disease.

Efficacy and dosage:

- Pilocarpine 2% lowers IOP in 1 hr and its effect lasts for 6–7 hr.
- Generally dosed three to four times a day.
- Reduces IOP by 20% to 25%.

Adverse effects:

- Major systemic side effects of this group are intestinal cramps, bronchospasm, and cardiac irregularities.
- Local side effects include stinging, lacrimation, pseudomyopia, browache, and a miosed pupil which can lead to constriction of visual field, and difficulty in focusing and adapting in dim light.
- Conjunctival thickening, iris cysts, cataract, intraocular inflammation and retinal detachment, may also be seen.

f. Hyperosmotic Agents

Hyperosmotic agents such as oral glycerin and intravenous mannitol are used to control acute episodes of elevated IOP. Other agents not commonly used are isosorbide and urea.

Mechanism of action: These agents increase the blood osmolality which creates an osmotic gradient between the blood and the vitreous humor, drawing water from the vitreous cavity and reducing IOP. Larger the dose and more rapid the administration, greater the reduction in IOP because of increased gradient.

Indications:

- Initial treatment of acute and extreme elevation of IOP, including angle closure glaucoma and certain secondary glaucomas.
- For preoperative preparation of select patients for intraocular surgery.

Contraindications:

- Patients with well-established anuria, severe dehydration, frank or impending acute pulmonary edema, and severe cardiac decompensation
- Hypersensitivity to any component of the preparations.

Efficacy and dosage:

Glycerol:

- Available as a 50% vol/vol (0.628g/mL) solution for oral administration.
- The usual dose is 1 to 1.5g/kg, which is about 2 to 3mL/kg body weight.
- Begins to lower IOP after only approximately 10 minutes.

Mannitol:

- Usual dose of mannitol for reduction of IOP is 0.5 to 2g/kg or 3-7ml/kg of body weight, given as an intravenous infusion of a 20% solution over a period of 30 to 60 minutes.
- Intravenous mannitol has an onset of action within 45 minutes.
- IOP lowering efficacy of mannitol is 15% to 30% and of other agents is 15% to 20%.

Adverse effects:

- Nausea, vomiting, headache, backache, acute congestive heart failure, and myocardial infarction are common adverse effects. The rapid increase in extracellular volume and cardiac preload caused by hyperosmotic agents may precipitate or aggravate congestive heart disease.
- Hyperosmolality and electrolyte disturbances may cause various central nervous system side effects, including thirst, chills, fever, confusion, and disorientation.
- Oral glycerol should be used with caution in diabetic patients because the blood glucose may rise after metabolism of the drug.

Preserved versus preservative-free drugs:

- Most glaucoma preparations are packaged in bottles that need to be discarded after 28-30 days. In order to prevent build-up of bacteria these preparations contain preservatives.
- The most commonly used preservative is BAC.
- Preservatives are often toxic to the surface of the eye, can disrupt the tear film and cause/exacerbate dry eye symptoms/ocular surface disease. The daily dosage of preservative in glaucoma medications is proportional to the symptoms of dry eye disease and the reduced quality of life.
- Some preparations contain alternative preservatives (eg. Stabilized oxychloro complex, Polyquaternium-1 or Ionic-Buffered System) that are considered “milder” than BAC.
- Some medications are available in preservative-free preparations. These are preferred over their preserved counterparts and should especially be considered in patients with dry eye syndrome, ocular allergy, meibomian gland dysfunction, contact lens wearers, patients

having corneal and conjunctival adverse reactions to antiglaucoma medication and pre-operative to trabeculectomy, e.g. Tafluprost unims.

The future looks promising as many other molecules are currently under development or preclinical evaluation for their potential effects in lowering IOP by increasing outflow or decreasing aqueous production.

Novel drug delivery mechanisms are also being developed to decrease the problems associated with conventional drug delivery. Some of these problems include:

- Rapid elimination
- Systemic absorption
- Epitheliotoxic
- Conjunctival toxicity and surgical failure
- Allergic reactions
- Dry eyes
- Pro-inflammatory

The newer mechanisms under research include:

- Prodrugs
- Aqueous formulations: increased viscosity
- Contact lenses
- Lyophilisates (Lyophilization of latanoprost on Teflon strips)
- Iontophoresis
- Sub-conjunctival and intracameral depots and inserts
- Erodible implants for the lower cul-de-sac
- Encapsulated cell technology
- Nanotechnology
- Si RNA: silence dsRNA in ciliary body; long acting
- Gene therapy & viral vectors

Recently, rho kinase inhibitor, ripasudil 0.4% have become available in India, which can be used as second or third line drug. It acts by increasing the conventional aqueous humor outflow. The most common side effect is conjunctival hyperemia.

To conclude, in addition to being knowledgeable about the efficacy and tolerability of various anti-glaucoma drugs, clinicians should also be familiar with the different formulations available, preservatives used, generics availability and compatibility to provide an effective glaucoma management. Therapy should be individualized to patients' needs and preferences.

Section - III

SPECIAL SITUATIONS

Part - A

Pseudoexfoliation Glaucoma

Pseudoexfoliation (PXF) is an age-related systemic disease characterized by progressive accumulation of extracellular, grey and white fibrillar proteinaceous material over various tissues. Dysregulated expression of Lysyl oxidase like-1 (LOXL1) and oxidative stress have been implicated in its pathophysiology, the exact cause however remains unknown. It is the most common cause of secondary open angle glaucoma worldwide. The term PXF differentiates it from "true-exfoliation" or a delamination of the lens capsule, which is seen typically in glass blowers.

Demographics

The reported prevalence of pseudoexfoliation in India is between 2-6%.[1-4] In Chennai Glaucoma Study (CGS), PXF was predominantly unilateral (59%) and was associated with glaucoma in 8.3%, ocular hypertension (OHT) in 7.2% and occludable angles in 8.3%. Prevalence increased with age and was higher in the rural cohort. In Andhra Pradesh Eye Disease Study (APEDS), glaucoma was seen in 3.02% subjects with PXF and was predominant with outdoor activities. Prevalence in Aravind Comprehensive Eye Survey (ACES) was 6% and glaucoma was seen in 7.5% of these subjects.

In CGS, 6% subjects (8/133) with PXF progressed to PXG at 6 years. All progressed subjects were OHT at baseline. Subjects with PXF had higher rates of cataract surgery than those without (43% vs 13%).

Incidence data in India is currently provided by Chennai Eye Disease Incidence Study (CEDIS). Incident PXF was seen in 2.03% (87/4228) with the rural incidence being much higher than urban (79.3% vs 20.7%).

Clinical Manifestations

Prevalence of PXF increases with age and is rare below 50 years. Exfoliative material is seen classically as dandruff-like material on the anterior lens capsule and pupil margins (Figure 1,2). A central disc of exfoliative material on lens capsule (conforming to pupil size) is surrounded by a clear intermediate zone and then an outer zone of exfoliative material (target sign).

Diagnosis is more obvious with dilated pupils (Figure 3,4). These signs may be difficult to elicit in pseudophakic eyes due to some washout of pseudo-exfoliative material. The prominent deposition in intermediate zone on the intraocular lens has been described to be different from the pattern seen in phakic eyes. (Figure 5) There is an association with nuclear cataract and lower endothelial cell density in PXF and PXG. It is a systemic disease and pseudo-exfoliative material can be found in many body organs including the conjunctiva, skin, heart, lungs, kidney, brain, and meninges.

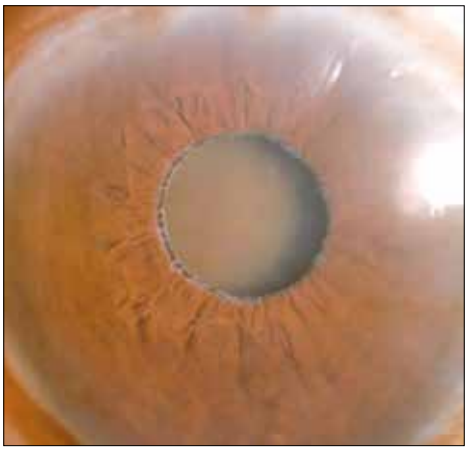

Figure 1: Whitish flecks deposition seen at the pupillary margin.

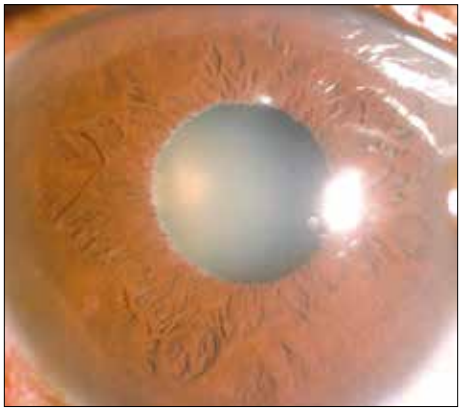

Figure 2: Pseudoexfoliation leading to pupillary ruff atrophy.

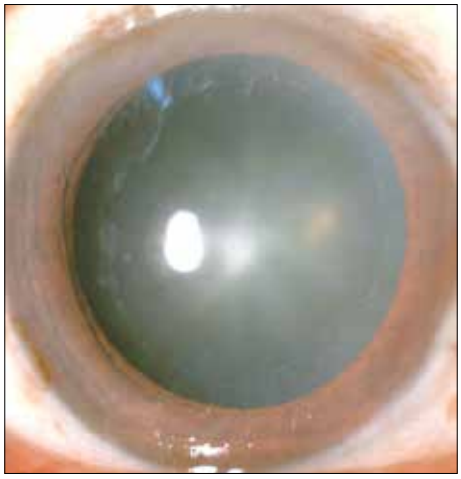

Figure 3: Exfoliative material deposition over lens surface.

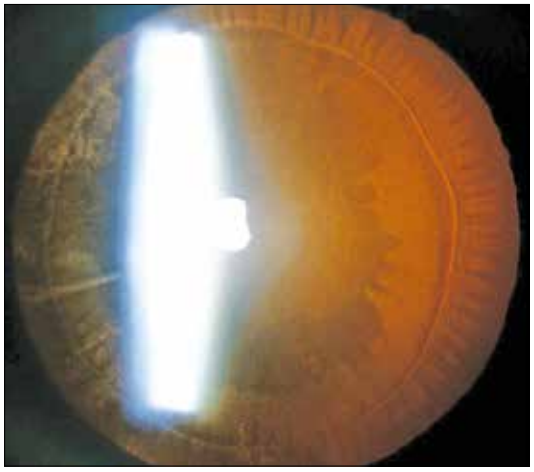

Figure 4: Target Sign formed by rubbing of iris over mid-peripheral lens surface leading to a clear intermediate zone.

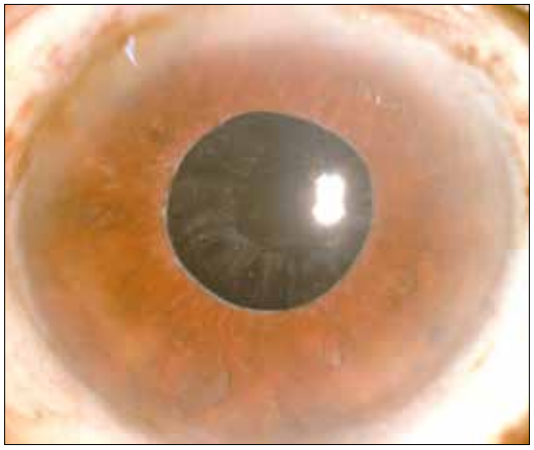

Figure 5: Exfoliative material deposition over the intraocular lens.

PXF, in isolation, is usually associated with open angles on gonioscopy, however weakened zonules can lead to angle closure. Gonioscopy may sometimes show exfoliation deposits on trabecular meshwork (Figure 6). A wavy pigment deposition above Schwalbe's line (Sampaolesi's line) and uneven pigment (salt and pepper pigmentation pattern) over the trabecular meshwork may be seen.

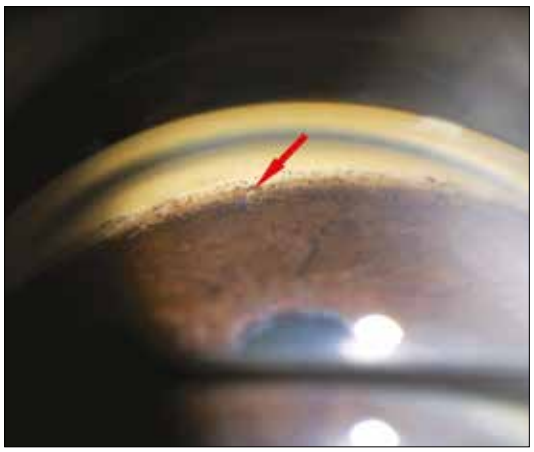

Figure 6: White flecks of exfoliative material deposited in angle. (Photo courtesy: Dr. Talvir Sidhu)

Elevation of IOP is due to clogging of trabecular meshwork both by PXF material and iris pigment release. For the same reason, significant IOP elevations can occur in a short period of time as compared to primary open angle glaucoma thereby warranting a close follow-up for IOP spikes. Higher IOP at baseline and history of heart attack at baseline have been associated with a greater likelihood of developing glaucomatous change in PXF cases.[5] **Subjects with PXG are reported to have greater mean IOP, worse diurnal IOP control, greater visual field loss at diagnosis and a rapid progression.** There are large 24 hour IOP fluctuations in PXG and so a single IOP reading may not be reflective of the true IOP status. In addition there is poor response to medications warranting surgical management in some cases. PXF is identified as a risk factor among others such as lower CCT, higher baseline IOPs, disc haemorrhages for rapid progression of glaucoma. PXF, besides other causes, should be excluded in patients with a unilateral rise of IOP.

Pseudoexfoliation may also be complicated by poor dilation of pupils (due to structural iris damage) and an unstable zonular support leading to lens subluxation, complications in cataract surgery, severe post-operative inflammation (due to defective blood aqueous barrier), pupillary block or angle closure.

Management

Due to high risk of developing glaucoma, patients of PXF are advised routine monitoring and follow-ups.[6] In case pressures are high, topical anti-glaucoma medications are required to reduce IOP. Generally prostaglandin analogues are considered first choice due to higher efficacy and longer duration of action which helps to reduce IOP spikes. In general, response to medications is poorer as compared to POAG. Monotherapy may not help as many cases require additional medications/laser to reduce IOP. Combination brimonidine-timolol or dorzolamide-timolol eye drops are reported to be as effective as prostaglandin analogues in blunting the diurnal curve.[7]

Laser Trabeculoplasty (Argon, SLT, micropulse) has been described as a useful adjunct to medical therapy with mixed results.[8,9] Lasers are usually effective but the effect may wane with time requiring follow-up and re-treatment.

Cataract surgery alone may lower IOP in PXF due to removal of accumulated debris in trabecular meshwork by irrigating fluid. However this effect may be temporary due to reaccumulation of debris with time. In eyes with angle closure, a mixed mechanism may exist for the development and progression of glaucoma, and the individual can benefit from laser iridotomy or early cataract extraction. In a report by the American Academy of Ophthalmology, 5 studies (total, 132 patients; follow-up, 34 months) showed phacoemulsification reduced IOP by 20% and glaucoma medications by 35%.[10] Careful preoperative evaluation for pupillary dilation and zonular loss/phacodonesis is necessary in all cases of PXF. Use of capsular tension rings (CTR) to stabilise capsular bag may be necessary. Post-operatively, increased inflammation wareants a higher frequency of steroid eye drops and, hence a watch on IOP spikes are necessary.

Triple procedure (phacoemulsification, trabectome and 360 degree trabecular aspiration) have shown good IOP lowering effects when seen over long follow-up with no additional side effects.[11]

Failing medical treatment, patients may require trabeculectomy either alone or in combination with cataract surgery if lens changes are present. Vitreous loss due to zonular damage, marked inflammatory reaction, hyphema, synechia formation, choroidal detachment, choroidal hemorrhage and cataract formation can complicate surgery in these eyes.[12]

Combined cataract surgery with trabeculectomy resulted in significant long-term reduction in IOP and glaucoma medication requirements in eyes with PXG. Combined procedures resulted in greater and more long-standing reductions in IOP and less glaucoma medication requirements along with a decrease in post-operative IOP spikes as compared to phacoemulsification alone.[13]

Non-penetrating glaucoma surgeries (Deep sclerectomy, Viscocanalostomy, Canaloplasty) although safer, but have been found inferior to trabeculectomy in reducing IOP.[14] XEN gel stent has shown promising results in management of PXG. Tube shunts as usual will be required in cases where conventional trabeculectomy is not amenable or has failed.[15]

Summary

- Careful slit lamp examination as signs of PXF are subtle.
- Examine the lens post-dilation as the peripheral zone is most easily evident in PXF.
- Frequent follow-ups as PXF cases are fast progressors (6 monthly).
- Rule out PXF in any case of unilateral glaucoma.
- Gonioscopy is necessary to rule out angle closure, especially in increasing damage or when intermittent spikes of IOP noted.
- Increased risk of surgical complications (esp.due to zonular weakness).

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Part - B

Juvenile Open Angle Glaucoma

Juvenile open angle glaucomas (JOAG) are the primary open angle glaucomas (POAG) that present early, between 10-40 years of age and have been described to have an autosomal dominant pattern of inheritance[1,2]. They generally present with very high IOP and have deep steep cups with diffuse visual field loss. While some consider the age of presentation as 5-35 years, others have considered those in 10-40 years age group as JOAG. While the age limits are arbitrary, what is important is understanding the varied presentation within this age group.

JOAG is uncommon in the general ophthalmic practice. In one study it was found that JOAG affects about 0.7% of patients referred for glaucoma evaluation in Caucasians[3]. While another study from a tertiary referral hospital in India found JOAG to represent 3.3% of all glaucoma admissions which indicates a 5 times greater prevalence of JOAG among Indians compared to Caucasians.[4] Demographically there is male preponderance that is seen in our clinics[5].

Not all JOAG present with very high IOP. The differences in clinical presentation may partly be attributed to the varied goniodysgenesis. On gonioscopy, almost 2/3 patients have some form of goniodysgenesis, either as high iris insertion, prominent iris processes or featureless angle such that the one cannot differentiate between the scleral spur and trabecular meshwork and this angle lacks the normal pigmentation[6]. In extreme cases, such an angle gives the appearance of a membrane described by Barkan or congenital glaucomas[7]. Sometimes there may be a combination of a featureless angle with high iris insertion. However, gonioscopy is known to be a gross representation of the histopathological anomalies affecting the angle. Tawara and Inomata observed the presence of a thick compact tissue in the trabecular meshwork samples of JOAG patients irrespective of whether they had an apparent goniodysgenesis or not[8].

While one would expect that among JOAG patients, those presenting at a younger age would have a more severe disease than those presenting at the age of 35 years, however this is not so and there can be great variability with younger patients presenting with not very high IOPs and having less severe visual field defect (VFD) while some patients may present at the age of 40 years with very high IOP and severe VFD.

The extent of variability is seen between the two eyes of the same patient[5]. Primary adult glaucoma is known to be asymmetric in its presentation, especially Primary angle closure glaucoma (PACG). But even JOAG may present with marked asymmetry at presentation with some presenting as unilateral glaucomas, in which case one must rule out secondary causes likes trauma, steroid use and rare cases such as Posner Schlossman Syndrome. In fact, almost 15% of these patients can present with unilateral glaucomatous optic neuropathy.

JOAG should be considered a diagnosis of exclusion after excluding secondary glaucomas like pigment dispersion glaucoma, traumatic glaucoma and steroid-induced glaucoma. PACG also needs to be excluded, especially in those JOAG variants with high insertion on gonioscopy as the therapy differs between the two conditions. Most important distinguishing feature in PACG is the convex iris configuration while JOAG patients have a regular iris configuration. Sometimes it may be difficult to distinguish a steroid induced glaucoma from JOAG as the latter also tend to have a high steroid responsiveness, or steroids may unmask a latent JOAG. Hence a proper history taking is a must in all cases.

Management

While some consider JOAG a developmental glaucoma, a disease to be managed surgically only, almost half of them can be controlled on medical therapy alone[9]. Medical treatment regime is similar as for any other adult primary glaucomas. Selective Laser trabeculoplasty has been found to lower the IOP in almost a third of JOAG patients, however, those with dysgenesis of the angle may not respond so well[10]. Many surgical approaches to lower IOP have been propagated, from bleb forming surgeries (trabeculectomy) to bleb-less surgery like visco canalostomy and goniotomy with varying success[11-13]. Trabeculectomy with low dose mitomycin provides better long term IOP than other surgical options in our experience.

Application of Mitomycin C during trabeculectomy amongst JOAG eyes has to be weighed judiciously. Though subconjunctival application of Mitomycin C during trabeculectomy gives lower IOP, it can lead to thin avascular blebs over time which can lead to bleb related infections, and the associated low IOP may be coupled with development of cataract. Prospective studies need to be conducted to confirm the long-term effects of Mitomycin C (MMC) applied during primary surgery amongst JOAG eyes.

Conclusion

JOAG is not so uncommon among our population. The classification of JOAG needs a relook as does its genetic associations. Therapy in this age group has to be chosen with care given the implications of therapy over the rest of the life of the individual.

Summary

1. By definition, JOAG is POAG presenting between 10-40 years of age.
2. Prevalence in India approximates 3.3%.
3. Characterised by very high IOPs, deep steep cups, diffuse visual field loss and apparent goniodysgenesis (67% patients).

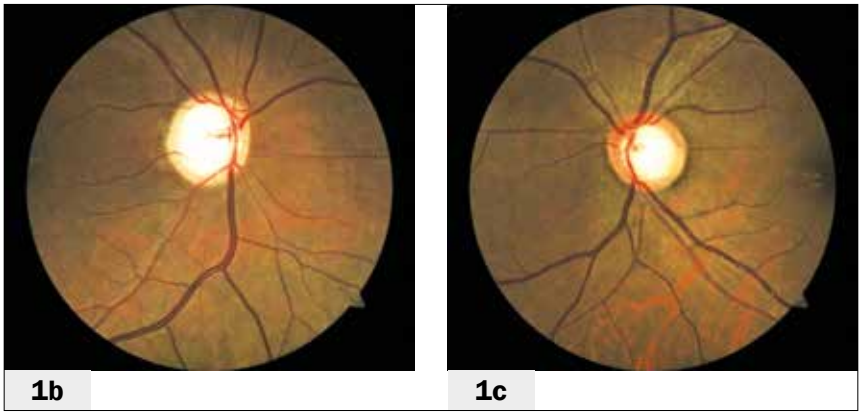
4. Is a diagnosis of exclusion.
5. May have asymmetric presentation between the two eyes.
6. Disease severity is not dependent upon age at presentation.
7. Primarily thought to be autosomal dominant, evidence is accumulating that the disease might be sporadic with a weak association with known genetic mutations of Myocilin C and CYP1B1.
8. Trabeculectomy with low dose MMC is the current gold standard for those requiring surgery.

Case 1:

A 15-year-old boy presented to our centre with complaints of finger nail trauma to the right eye 2 days back followed by redness. On examination, the visual acuity was 6/6 OU. He had a small subconjunctival hemorrhage in the right eye, both corneas clear, deep anterior chambers, and clear lenses. Applanation tonometry was OD 38 mmHg and OS 40 mmHg. Central corneal thickness was OD 536µ and OS 540µ. On gonioscopy, both eyes had prominent iris processes (Figure 1-A). Fundus evaluation showed a circular disc with cup-disc ratio 0.85:1 and circumferential neuroretinal rim thinning (Figure 1-B, C). There was no family history of glaucoma nor any systemic/local steroid use. Hence a diagnosis of both eyes JOAG was made, and the patient was started on immediate medical management. A Humphrey 30-2 SITA Standard perimetry was done which did not show any visual field defects (Figure 1-D, E).

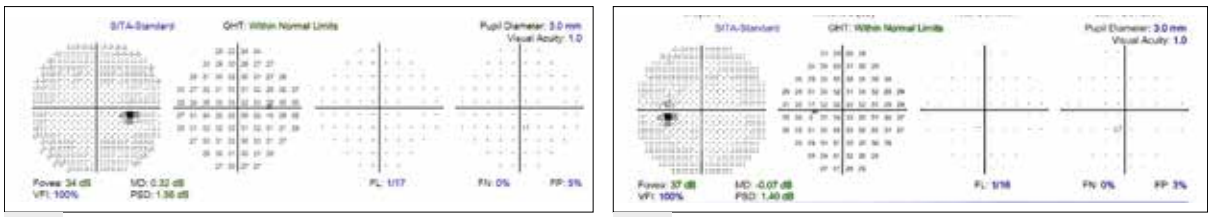
The child was started on tablet acetazolamide 250mg stat, topical latanoprost 0.005% HS and timolol maleate 0.5% bd. The child was reviewed after three days, and the IOP had fallen to 20 mmHg both eyes. Planning a target IOP of 14-16 mmHg, topical brimonidine 0.1% bd was added. Review after 2 weeks showed the child to have an IOP of 16 mmHg both eyes. Patient was managed medically and asked to come for regular follow-up.

Figure 1(A): Gonio-photograph showing prominent iris processes.



1b 1c

Figure 1(B,C): Disc photograph of OD and OS showing a cup-disc ratio of 0.85:1 with circumferential neuro-retinal rim thinning



1d 1e

Figure 1 (D,E): Humphrey visual field 30-2 SITA Standard report showing no visual field defects.

Case 2:

A 15-year-old boy presented to our centre with complaints of decreased vision in right eye for 6 months. He was diagnosed at an outside centre to have glaucoma and was on topical latanoprost 0.005% HS, fixed dose combination of timolol 0.5% and brimonidine 0.15% BD, and dorzolamide 2% TDS. However, the compliance was poor due to the patient's socioeconomic status.

On examination, the visual acuity was 6/18 OD and 6/6 OS, with relative afferent pupillary defect in the OD. Both corneas were clear, anterior chambers were deep, and lenses clear. Applanation tonometry was OD 24 mmHg and OS 20 mmHg. Central corneal thickness was OD 486µ and OS 490µ. On gonioscopy, both eyes showed anterior iris insertion (Figure 2-A). Fundus evaluation showed OU vertically oval disc with near total cupping in OD and cup-disc ratio 0.9:1 with circumferential neuroretinal rim thinning in OS (Figure 2-B, C). There was no family history of glaucoma nor any systemic/local steroid use. A diagnosis of both eyes JOAG with advanced glaucomatous optic neuropathy was made. A Humphrey 30-2 SITA Standard perimetry was done which showed both eyes bi-arcuate scotoma (Figure 2-D, E). Given the target IOP of 10-12 mmHg and the patient's socioeconomic status, he was advised surgical management.

He underwent trabeculectomy with 0.02% subconjunctival MMC for 2 minutes in OD followed by the OS. On post-operative day-1 (POD-1), the bleb was diffuse with an IOP of 8 mmHg OU. On POD-7, the IOP was OD 10 mmHg and OS 12 mmHg. Post-operative 6 months, his IOP was 12 mmHg both eyes on no medications.

Figure 2 (A): Gonio-photograph showing anterior iris insertion.

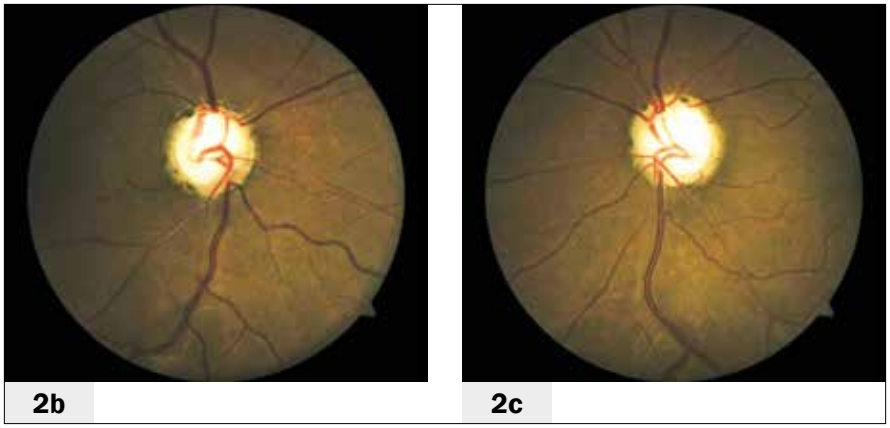


Figure 2 (B, C): Disc photograph of OD showing a near total cupping and OS cup-disc ratio of 0.9:1 with circumferential neuro-retinal rim thinning.

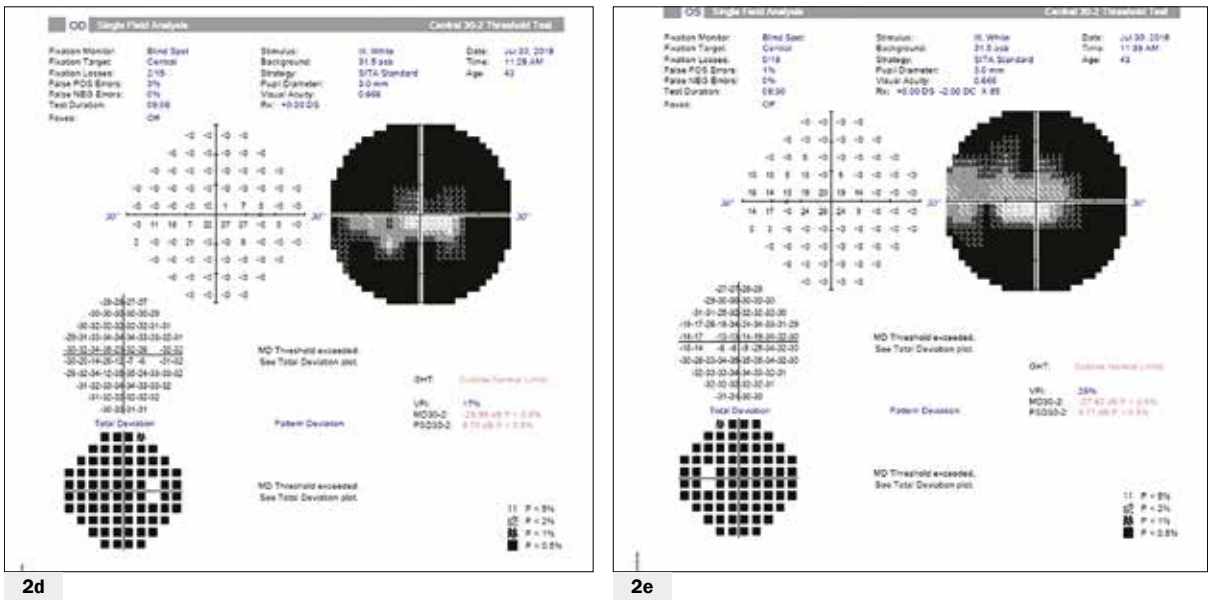


Figure 2 (D, E): Humphrey visual field 30-2 SITA Standard report showing bi-arcuate visual field defects, in both eyes.

Table 1: Differentiating features between JOAG and POAG

Juvenile open angle glaucoma	Primary open angle glaucoma
Age group: 10-40 years of age	>40 years of age
May have asymmetric presentation in up to 25%	Mostly have symmetric presentation
Very high baseline IOPs (commonly >30 mmHg)	Moderately high baseline IOP
Angles may show varying levels of dysgenesis: High iris insertion/ prominent iris processes/ featureless angle	Widely open angles
Optic discs may show deep steep cups and circumferential rim thinning	Cups may be shallower and neuroretinal rim may show uniform thinning/focal notching
Though management options are the same, JOAG is more refractory to treatment	Better treatable than JOAG
Related to MYOC and CYP1B1 genes.	Related to MYOC, OPTN, WDR36 genes.

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Part - C

Normal Tension Glaucoma

Normal tension glaucoma (NTG) is defined as a chronic progressive optic neuropathy despite the intraocular pressure (IOP) being in the statistically normal range. The optic nerve damage and visual field loss is characteristic of that seen in patients with glaucoma related to chronically elevated IOP.[1]

Salient features:
Asymptomatic until advanced visual field (VF) loss occurs or fixation is involved.
Diagnosis of exclusion.

Epidemiology

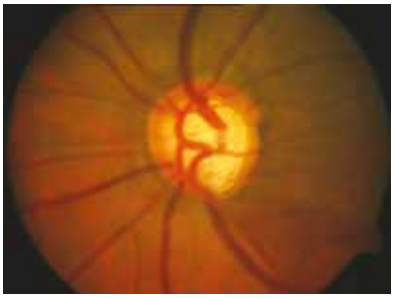
In a population based review, the calculated mean proportion of NTG was larger in Asia (76.3%) than in white population (33.7%).[2] It is the most common form of glaucoma in East Asian countries like Korea and Japan.

Pathophysiology

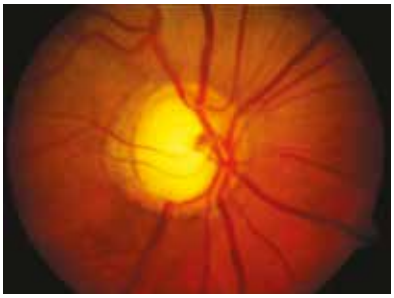
- Both IOP dependent and independent mechanisms have been proposed.
- IOP dependent mechanisms are supported by Collaborative Normal Tension Glaucoma Study (CNTGS) which showed favourable effect of IOP reduction on progression of VF.[3] However progression is seen despite lowering of IOP suggesting involvement of non-IOP factors as well.
- IOP independent mechanisms proposed are perfusion instability, hemodynamic crises, hypercoagulability, systemic hypotension with nocturnal dips, carotid artery disease, Flammer syndrome, oxidative stress and low intracranial pressure.
- Association with obstructive sleep apnoea, migraine and Alzheimer's disease suggest a vasculopathic etiology.
- A number of genes, mutations, and genetic variants of NTG have been investigated.[4]

Clinical Diagnosis

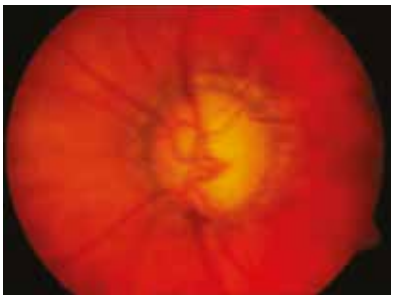
- Detailed history including targeted questions towards systemic conditions, haematological crisis in past, injury or steroid abuse.
- Family history of similar condition and the pattern of inheritance.
- Slit lamp evaluation to exclude other causes of glaucoma.
- Diurnal variation test (DVT) to rule out IOP spikes.
- Pupillary evaluation to elicit relative afferent pupillary defect (RAPD) in asymmetrical disease.
- Optic nerve head (ONH) Evaluation-Characteristic changes include inferior/infero-temporal thinning, prominent beta zone atrophy and disc haemorrhages. The residual neuroretinal rim (NRR) is generally pink.



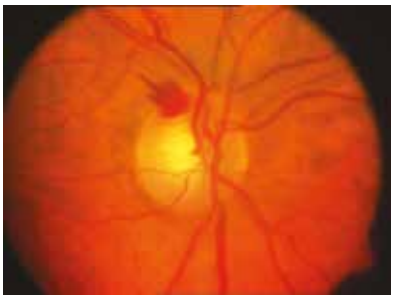
(1) Focal Ischemic



(2) Myopic



(3) Senile Sclerotic



(4) Disc Hemorrhage

Figures 1 to 4: Characteristic optic nerve head changes

- Colour vision evaluation - typically normal in NTG.
- Migraine, disc haemorrhage, female gender, vasospastic disorders and racial heritage are detected as risk factors for progression.[5]

Investigations

Central corneal thickness (CCT): To avoid erroneous assumption of IOP being in normal range in patients with thinner than average CCT.

VF analysis: VF defects in NTG tend to be focal, deeper and closer to fixation. A smaller scotoma closer to fixation may be missed on 24-2 but detected on 10-2 protocol. Frequent fields in the initial evaluation will help in detecting progression and its rate. In CNTGS, patients with

field defect threatening fixation did not seem to worsen more frequently or more rapidly than others.[5]

Disc stereophotography: Baseline documentation will help to determine any structural progression.

Other Investigations

Ambulatory 24-hour BP monitoring: Nocturnal dips in blood pressure (BP) by >20% is a significant risk factor for optic disc hemorrhage in NTG which is in turn a potent predictor of VF progression.[6]

Colour Doppler imaging of common carotid artery: Vascular factors are actively involved in NTG and its related diseases. Mechanisms proposed are oxidative stress, vasospasm and endothelial dysfunction. Mean ocular perfusion pressure (OPP) can be calculated as 2/3 of the mean arterial BP – IOP; where mean arterial pressure =diastolic BP + 1/3 (systolic BP – diastolic BP).[7] It determines the perfusion of the ONH. On comparing progressing and non-progressing NTG patients, it was found that the progressing group had wider 24-hour fluctuations in mean arterial pressure and mean OPP.[7]

Obstructive sleep apnea workup: In susceptible individuals, this will help in treating the underlying condition.

Neuroimaging: Neuroophthalmic conditions for the occurrence of cupped disc should be sought for some causes. Indications for neuroimaging of patient with a cupped ONH include vertically aligned field defects, NRR pallor in excess of cupping, hypothalamic pituitary dysfunction, presence of neurological abnormalities, RAPD, patient <50 years of age, asymmetrical loss of colour vision or visual acuity <20/40.[8] Discrepancy in ONH and VF should also prompt neuroimaging.

Genetic testing: In patients with ONH cupping, genetic tests for Leber's Hereditary Optic Neuropathy (LHON) is recommended in sudden loss of central vision, bilateral profound vision loss, centrocecal scotomas, maternal family history or relative preservation of pupil responses and for autosomal dominant optic atrophy (ADOA) in progressive visual loss over decades, color vision deficit, NRR pallor and disc changes in younger family members.

Differential Diagnoses

Other forms of glaucoma

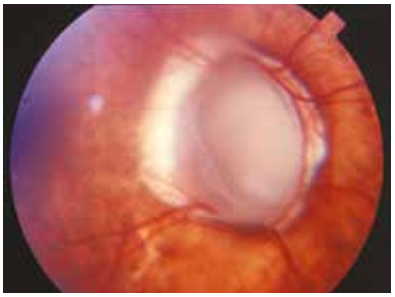
- Primary open angle glaucoma (missed IOP spike /erroneously low reading due to thin CCT)
- Secondary glaucoma like steroid-induced glaucoma, burnt out pigment dispersion glaucoma, inflammatory glaucoma with damage in the past.
- Misdiagnosed primary angle closure glaucoma.

Congenital optic disc anomalies (Figures 6,7)

- Morning glory syndrome
- Optic disc pit
- Coloboma involving the ONH
- Tilted optic disc
- Megalopapilla
- Optic nerve hypoplasia
- Superior Segmental Optic Hypoplasia

(5) AION

(6) Optic Nerve Pit



(7) Disc Coloboma

Figures 5 to 7: Non-Glaucomatous cupping and Congenital disc anomalies

Acquired conditions

- Ischemic optic neuropathy (Figure 5)
- Compressive optic neuropathy due to tumours like meningioma, pituitary adenoma.
- Toxic optic neuropathy like methanol toxicity
- Endocrine conditions or empty sella syndrome
- Genetic conditions like ADOA, LHON.

Treatment

Treatment includes IOP lowering with management of associated systemic conditions. Natural course of NTG revealed that half of the eyes show recognisable deterioration within 5-7 years, but most progress slowly and there is a broad spectrum in the rates.[9] When IOP was lowered by 30% from baseline, 12% of treated eyes reached the end points defined for disease progression as opposed to 35% of untreated eyes. However, there were some patients who continued to progress even after 30% IOP reduction.[3]

Medical management with topical IOP lowering agents is the first-line of treatment. Monocular trial can be employed to assess the response. Prostaglandin analogues and Brimonidine are the current choice of treatment.[10,11] Various neuroprotective agents are being evaluated but substantial evidence is lacking.

Selective laser trabeculoplasty (SLT) achieves an additional 15% IOP reduction in a single session while using 27% less medication at 1 year. A higher pre-SLT IOP and a greater IOP reduction at 1-week post-SLT have been found as predictors of a successful outcome.[12]

Surgical options include filtering surgery alone in the form of trabeculectomy with antifibrotic agent or combined with cataract surgery in presence of visually significant cataract is recommended when target IOP is not achieved with non-surgical means.

Summary

- NTG is a progressive optic neuropathy.
- IOP is the only known modifiable risk factor at present.
- Comprehensive examination including CCT, VF assessment and DVT is necessary.
- It is a diagnosis of exclusion. Hence, ruling out NTG masquerades is important since some may be associated with life threatening conditions like Intra cranial tumours.

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Section - IV

MANAGEMENT ALGORITHMS AND CASE STUDIES

Part - A: Case Study: Ocular Hypertension

A 45-year-old male presented with baseline IOP of 24 mmHg right eye (OD) and 26 mmHg left eye (OS) with a central corneal thickness of 530 and 535 microns respectively. Gonioscopy showed wide open angles. Fundus examination showed a vertical cup disc diameter ratio of 0.6 in both eyes (Figure CS1-1) with healthy neuroretinal rim in both eyes. The visual fields were within normal limits (Figure CS1-2). There was no associated systemic illness or family history of glaucoma.

The IOP readings were repeated 3 times (24/24, 24/26, 24/25 mmHg) and a baseline retinal nerve fibre layer OCT was done, which did not reveal any abnormality in the retinal nerve fiber layer (Figure CS1-3).

How would you manage this patient ?

This patient was diagnosed as a case of OHT and was asked to follow-up on an annual basis.

Patients with OHT can be treated in two possible ways.

Option 1 - Follow-up the patient every year with serial disc photographs and visual fields (OCT if available) and start treatment only if there is development of retinal nerve fiber layer defect or thinning of the neuroretinal rim and/or appearance of persistent visual field defect.

Option 2 – Start on medical therapy with a single drug or perform Selective Laser Trabeculoplasty (SLT) - If patient has a higher risk of progression (IOP > 25, thin CCT, positive family history of glaucoma, pseudoexfoliation, large cup-disc ratio, one-eyed patient, higher pattern standard deviation values on perimetry and systemic disease such as diabetes, hypertension, cardiovascular disease, etc.) In eyes with OHT, treatment can also be initiated, if the baseline IOP is more than 30 mmHg, after rechecking the IOP once with GAT.

The physician should discuss with the patient and either of these approaches may be followed – the latter one suits patients who are highly apprehensive about the development of glaucoma or cannot come for regular follow-up.

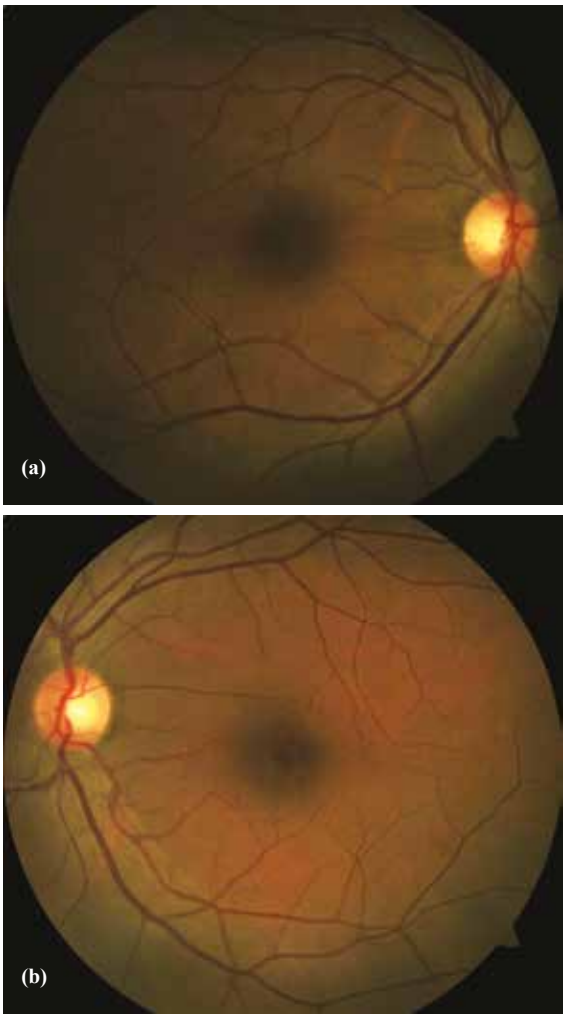


Figure CS1-1: Fundus picture of Right eye (a); Left eye (b)

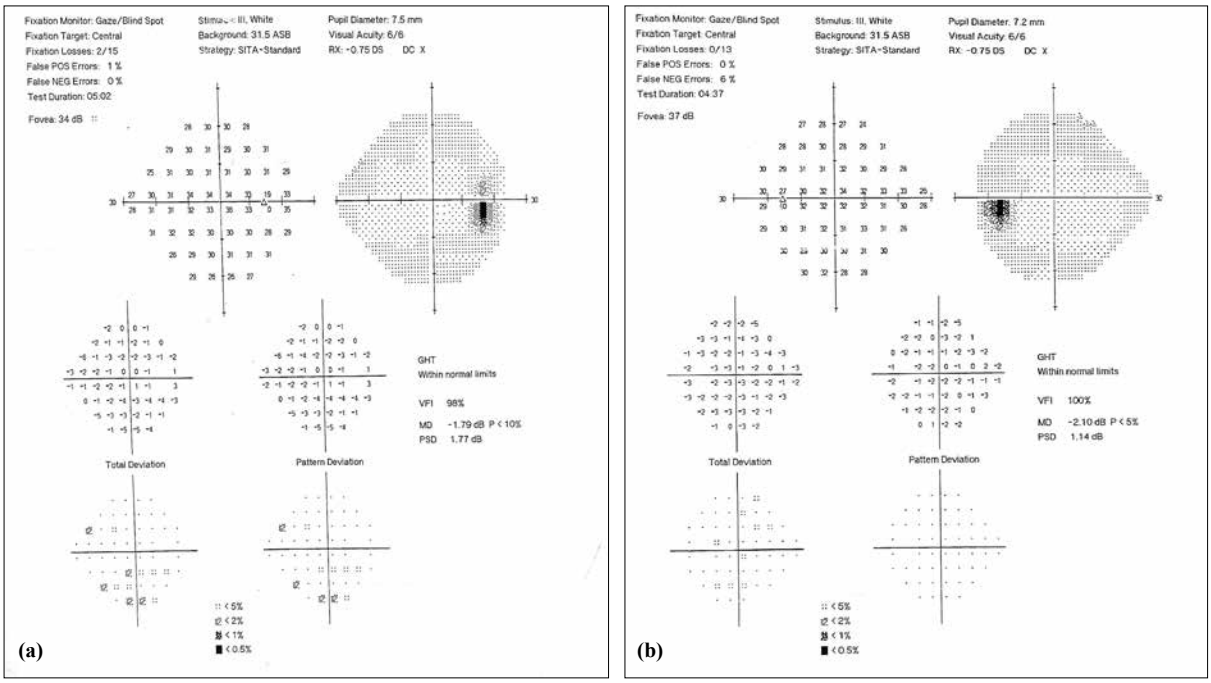


Figure CS1-2: Visual field of Right eye (a); Left eye (b)

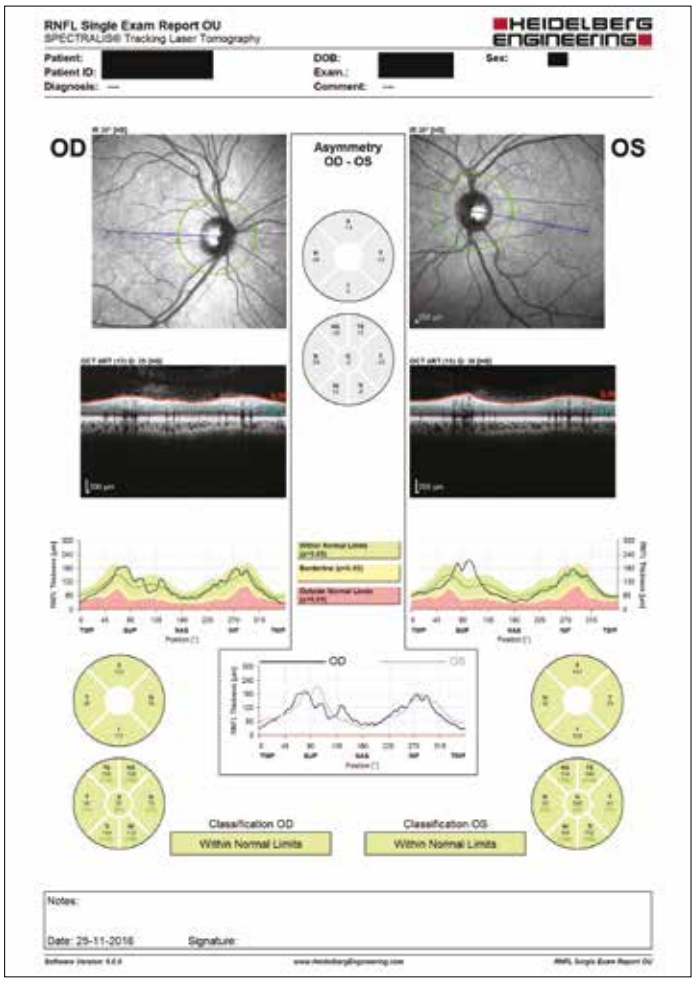
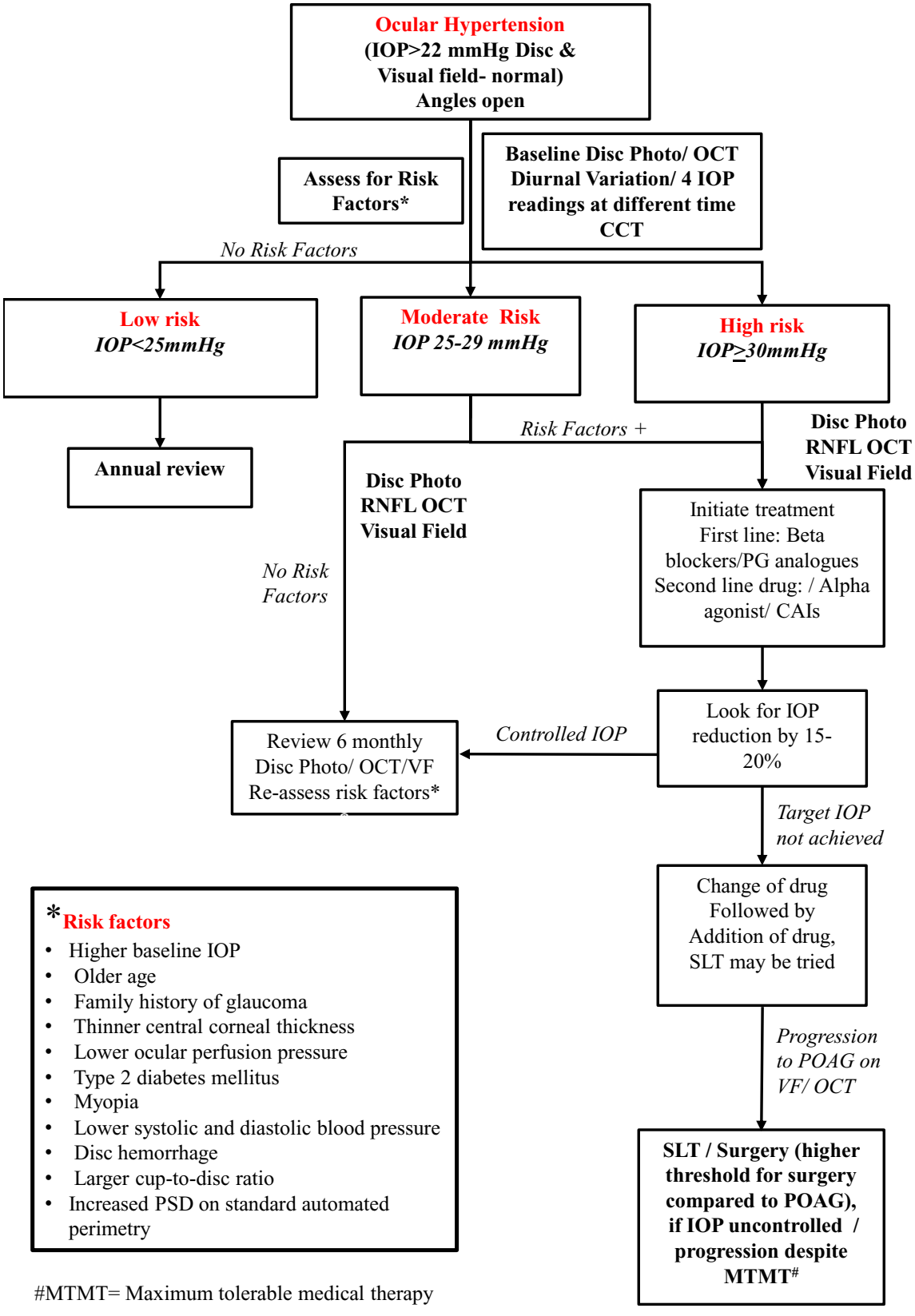


Figure CS1-3: OCT showing a healthy Retinal Nerve Fiber Layer

Part - B: Management Algorithm for Ocular Hypertension



*Risk factors

- Higher baseline IOP
- Older age
- Family history of glaucoma
- Thinner central corneal thickness
- Lower ocular perfusion pressure
- Type 2 diabetes mellitus
- Myopia
- Lower systolic and diastolic blood pressure
- Disc hemorrhage
- Larger cup-to-disc ratio
- Increased PSD on standard automated perimetry

#MTMT= Maximum tolerable medical therapy

Part - C: Case Study: Pre-Perimetric Glaucoma

A 45-year-old man with NIDDM and family history of glaucoma presented for fundus evaluation for diabetic retinopathy. He had vertical CDR of 0.8:1 in both eyes (Figure CS2-1). The IOP at baseline was 24 mmHg OD and 23 mmHg OS respectively. The CCT was 530 and 538 µm in OD and OS respectively. Gonioscopy revealed open angles. The visual fields were normal in both eyes (Figure CS2-2) and there was no retinopathy.

How would you manage this patient ?

The patient underwent dilated fundus photography and RNFL OCT (Figure CS2-3), both of which revealed inferior RNFL defect in right eye. A diagnosis of pre-perimetric POAG was made and the patient was started on Latanoprost eye drops at night. IOP after 4 weeks ranged from 15-18 mmHg and the patient was asked to follow-up after 6 months for repeat testing of IOP, visual field and OCT. Annual fundus examination for diabetic retinopathy was also recommended with appropriate control of blood sugar levels.

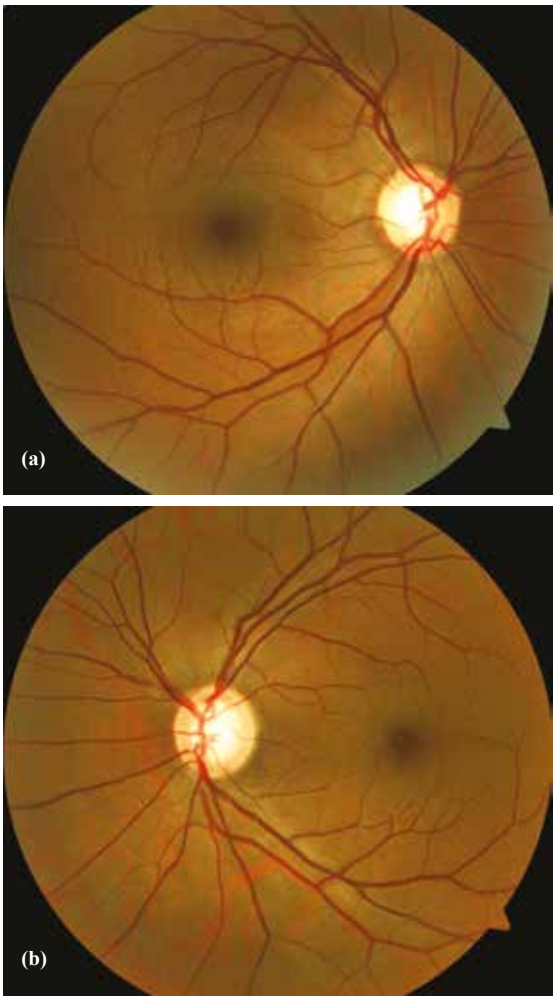


Figure CS2-1: Fundus picture of Right eye with inferior RNFL defect (a); Left eye (b)

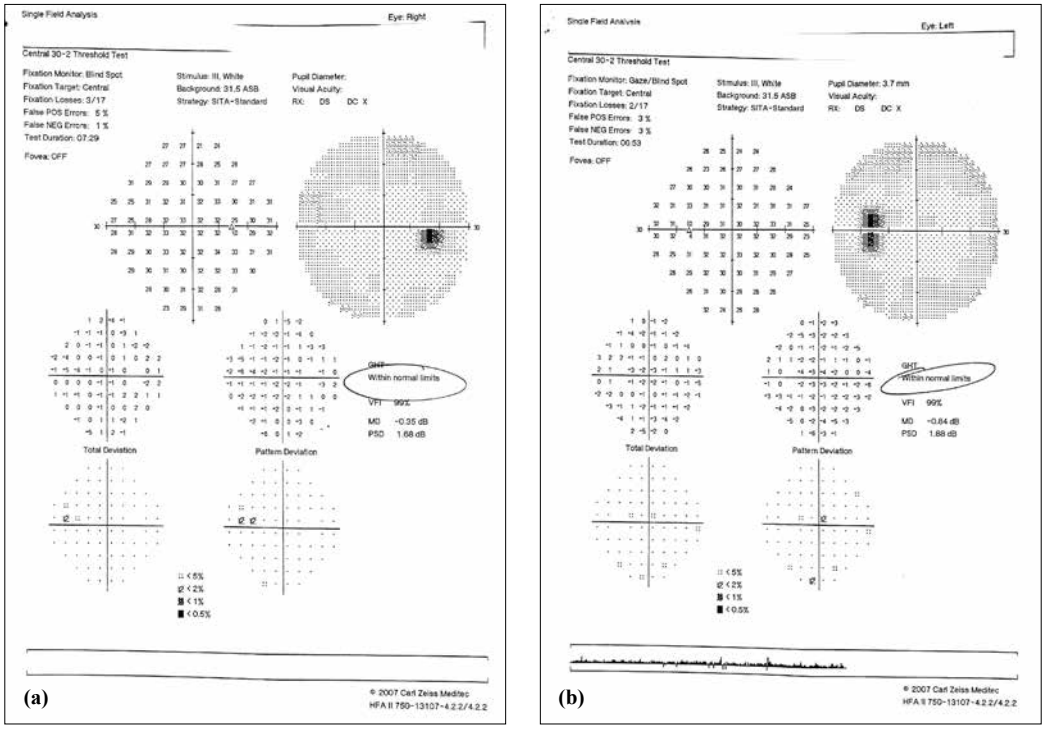


Figure CS2-2: Visual field of Right eye (a); Left eye (b) both are within normal limits

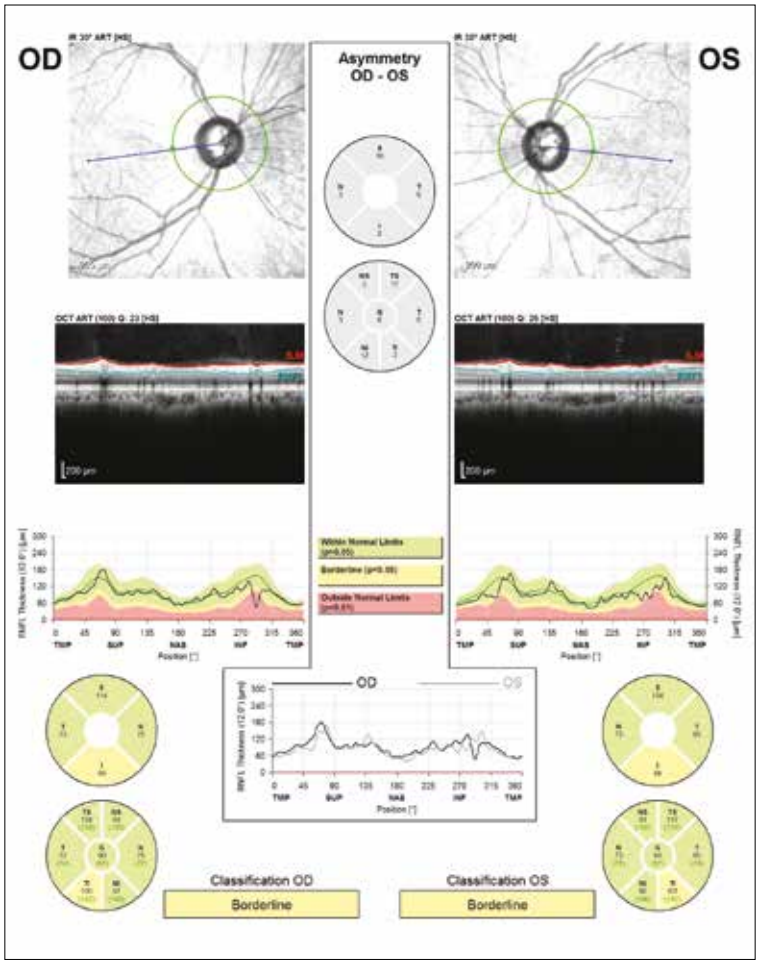


Figure CS2-3: RNFL OCT of both eyes with right eye showing inferior RNFL damage.

Part - D: Case Study: Early POAG

A 57-year-old woman presented with IOP of 22 mmHg OD and 24 mmHg OS. On diurnal variation, the IOP peak was seen at 7am – 24 and 26 mmHg in OD and OS respectively. She had CCT of 498 and 495 in OD and OS. She had a CDR of 0.6 and 0.7 in OD and OS (Figure CS3-1, 3-2). OCT showed inferior RNFL thinning in left eye (Figure CS3-4), with inferior rim thinning in OS. HVF 30-2 SITA Std showed a large nasal step with a paracentral scotoma (Figure CS3-3). There was no family history of glaucoma. Patient was diabetic (NIDDM) since 1 year and hypertensive (HT) since 3 years with good control on Atenolol.

What is the treatment for this patient ?

The target IOP of any glaucoma patient should as a general rule be always be less than 18 mmHg at all times during the day at all follow-up visits. In this patient with NIDDM and HT with lower CCT values (normal 520 µm) and already on systemic beta blocker, a target IOP around 15-16 mmHg would be appropriate. The first-line of treatment is to start a prostaglandin analogue (Latanoprost, Travoprost, Bimatoprost or Tafluprost) at night since the IOP peaks at 7am. Since the patient is using a systemic beta blocker, topical beta blockers should be avoided. The IOP should be rechecked after 6 weeks and brimonidine/brizolamide added (6am-6pm) if target IOP is not reached. The patient must be instructed how to instil eye drops with digital occlusion of tear duct.

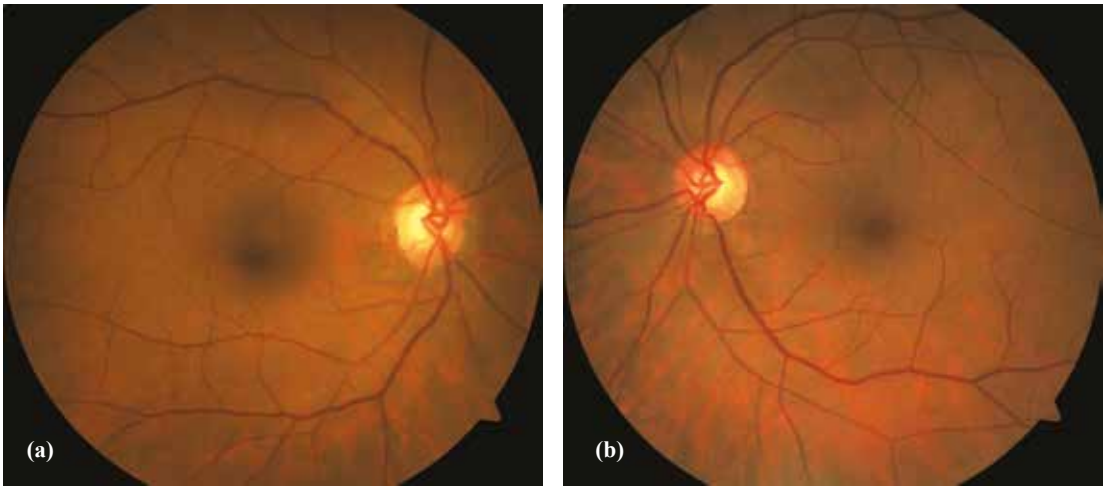


Figure CS3-1: Fundus picture of Right eye (a); Left eye (b)

Figure CS3-2: Color picture of right eye showing inferior loss of RNFL.

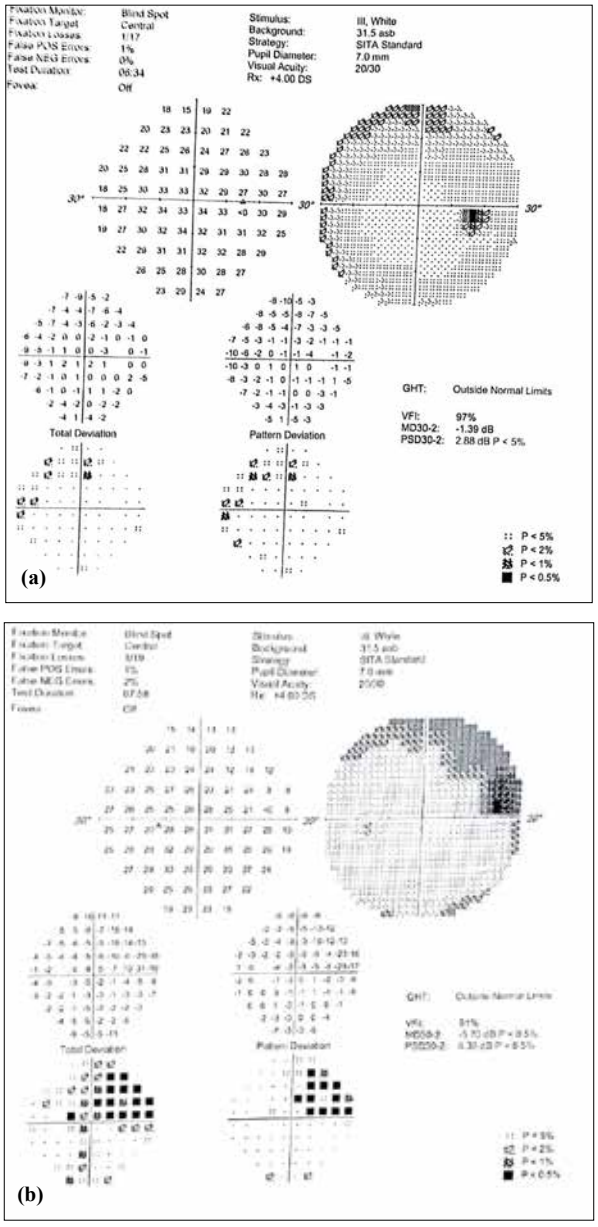


Figure CS3-3: Visual field of Right eye (a); Left eye (b)

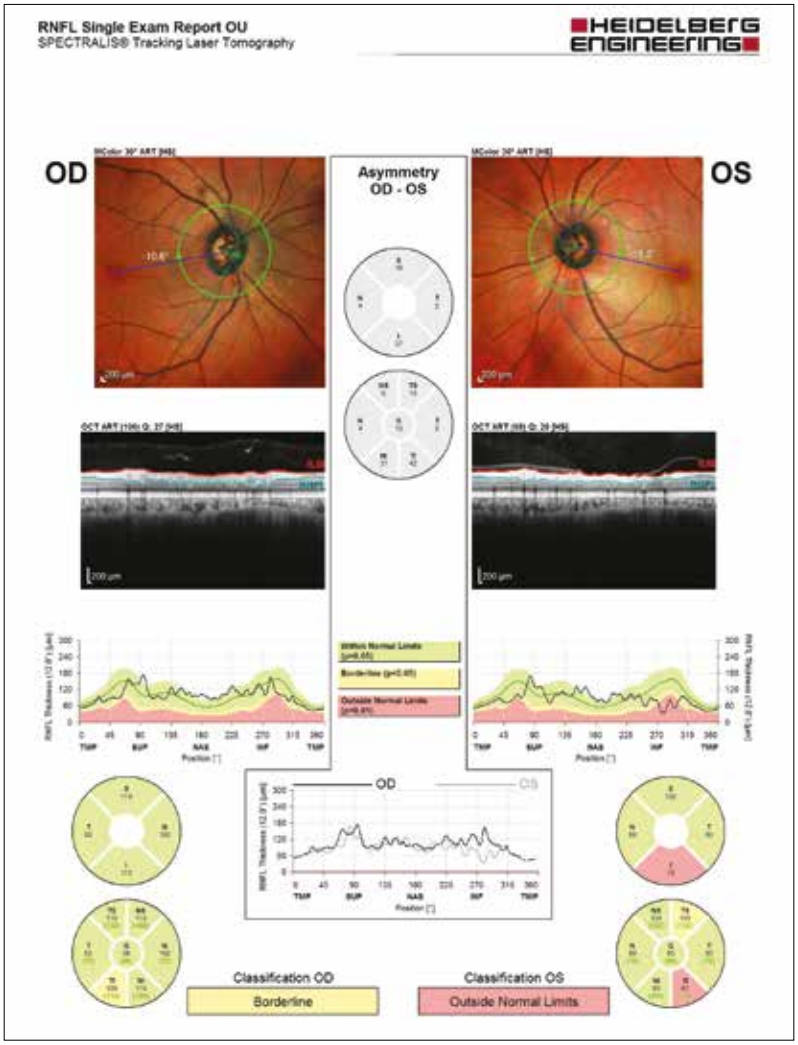


Figure CS3-4: RNFL OCT of both eyes.

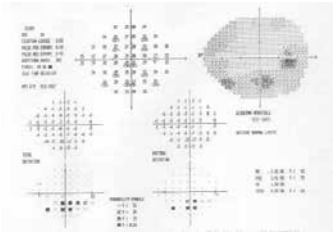
Part - E: Management Algorithm for Early POAG

VCDR <0.7

Early POAG
VCDR<0.7
Visual field- early defect not within 10 degrees of fixation
MD better than -6dB

DV at baseline/ 4 IOP during day.
Baseline Disc Photo/ OCT

Start medical therapy- First line
Beta blocker/ Prostaglandins
Or
Primary SLT*
Set Target IOP (16-18mmHg)
Check IOP at 4-6 weeks



Early visual field defect.
MD more than -6dB

Target IOP not reached and/or confirmed progression noted on RNFL OCT or Visual Field

Target IOP reached

IOP reduced ≥15-20%

IOP reduced <15-20%

Add medication/ trial of SLT

Ensure compliance^
Switch medication/ trial of SLT

Target IOP not reached on MTMT #

6 monthly Review

IOP
Structural tests (Disc Photo/OCT)
Visual Fields

HVF/OCT
Progression noted

Trabeculectomy**

Yes
Modify therapy
Review in 1-2 months
Rule out other causes of progression$

No
Review 6 monthly

***Selective laser trabeculoplasty** can be added/ done at any stage.

****Indications of Trabeculectomy**

- IOP not controlled on maximum tolerable medical therapy (MTMT)
- Progression despite maximal medications
- Poor tolerance to medications
- Not able to afford medications

$ **Other causes of progression**: steroid use, concurrent neurological disease, nocturnal hypotension, lifestyle changes.

^Ensure compliance to adherence by asking the number of bottles purchased, time of instillation, check technique of instillation.

#MTMT= Maximum tolerable medical therapy

Part - F: Case Study: Moderate Glaucoma

A 55-year-old male who presented to OPD with complaints of eye irritation was found to have enlarged cup:disc ratio and referred for glaucoma evaluation. His intraocular pressure was 24 mmHg in OD and 22 mmHg in OS taken at 11am. His central corneal thickness (CCT) was 500 µm in both eyes and angles were open. Fundus evaluation showed large inferior neuro-retinal rim notch in OD and smaller notch in OS (Figure CS4-1). Patient had corresponding large superior arcuate defect in OD and a small arcuate scotoma in OS (Figure CS4-2). The patient was labelled as a case of moderate POAG. There was no family history of glaucoma. Patient did not have any systemic medical illness.

How would you treat this patient ?

The target IOP should be around 14 to 15 mmHg. The patient was started on combination therapy with 2 medications (travoprost and timolol) in the form of 1 drop early morning at 6 am. The IOP was 16-18 mmHg after 4 weeks and dorzolamide eye drops were added at 9 am and 9 pm which lowered the IOP to target. The patient was asked to follow-up every 6 months with perimetry and OCT to detect progression. If progression is detected, the target IOP and medical management will be re-evaluated.

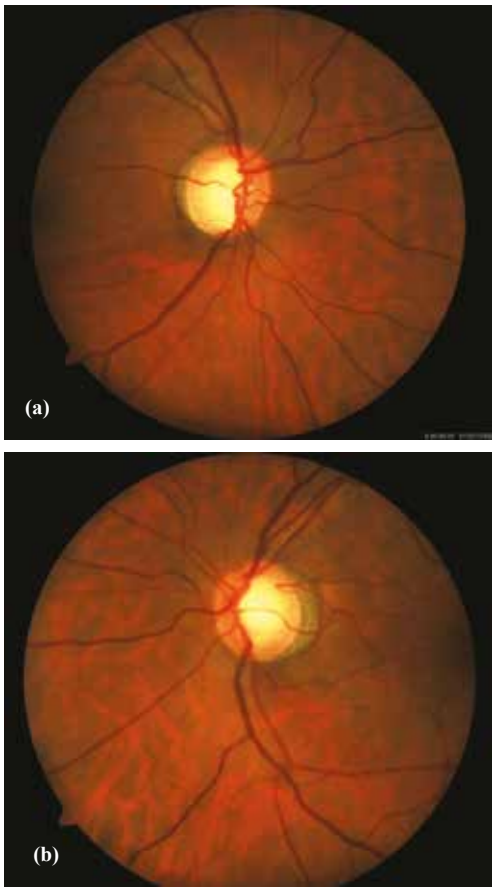
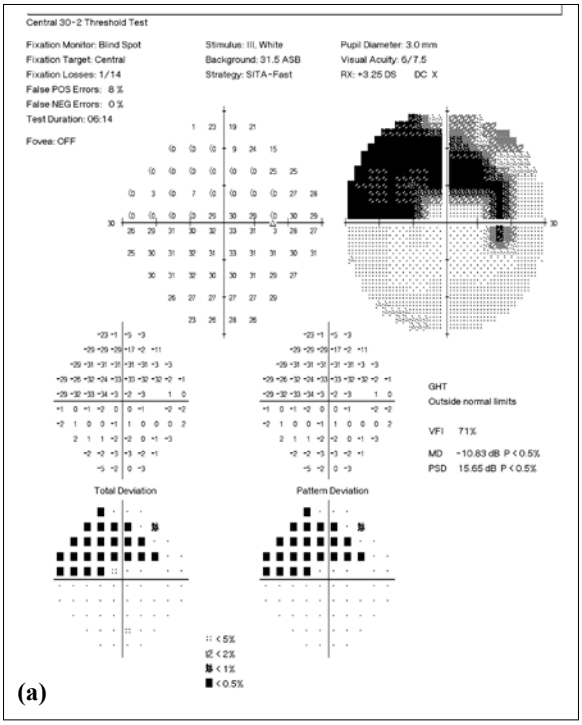


Figure CS4-1: Fundus picture of Right eye (a); Left eye (b)



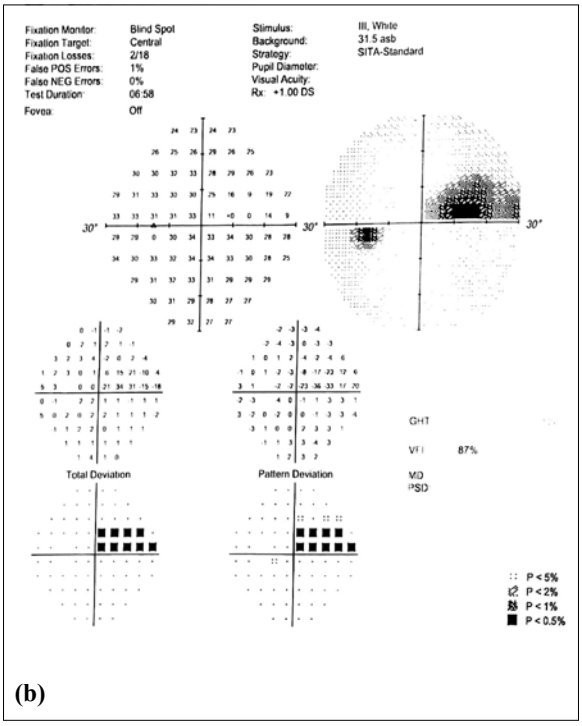
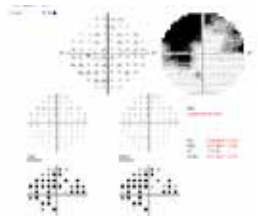


Figure CS4-2: Visual field of Right eye (a); Left eye (b)

Part - G: Management Algorithm for Moderate POAG

VCDR 0.7-0.85

Moderate POAG
VCDR 0.7-0.85
Visual fields- scotoma in only 1 hemifield, not within 10 degrees of fixation
MD -6 to -12 dB



Scotoma in 1 hemifield
MD -6 dB to -12 dB

DV at baseline/ 4 IOP during day.
Baseline Disc Photo/ OCT

Start medical therapy- First line Prostaglandins followed by Beta Blockers
Second line: CAI/ Alpha agonist
Or
Primary SLT*
Set target IOP (14-16mmHg)
Check IOP at 4-6 weeks

Target IOP not reached and confirmed progression noted on RNFL OCT or Visual Field

IOP reduced ≥15-20%

Add medication/ trial of SLT

IOP reduced <15-20%

Ensure compliance^
Switch medication/ trial of SLT

Target IOP not reached on MTMT #

Trabeculectomy**
(with antimetabolites)

Target IOP reached

4 monthly Review

IOP
Structural tests (Disc Photo/OCT)
Visual Fields

HVF/OCT
Progression noted

Yes
Modify therapy
Review in 1-2 months
Rule out other causes of progression$

No
Review 4 monthly

***Selective laser trabeculoplasty** can be added/ done at any stage.
****Indications of Trabeculectomy**
- IOP not controlled on maximum tolerable medical therapy (MTMT)
- Progression despite maximal medication
- Poor tolerance to medications
- Not able to afford medications

$ **Other causes of progression**: steroid use, concurrent neurological disease, nocturnal hypotension, lifestyle changes.
^Ensure compliance to adherence by asking the number of bottles purchased, time of instillation, check technique of instillation.

#MTMT= Maximum tolerable medical therapy

Part - H: Case Study: Advanced Glaucoma

A 60-year-old male presented with IOP of 28 mmHg in both eyes with a vertical cup-to-disc ratio of 0.9 in both eyes (Figure CS5-1). The BCVA in right eye was 6/18 and left eye was 6/6. The CCT was 530 and 524 microns in right and left eye respectively. Gonioscopy revealed open angles. HVF showed advanced visual field defects in both eyes with less than 10 degree field in right eye and less than 20 degree in left eye (Figure CS5-1).

How do you manage this patient?

This patient with advanced glaucoma requires a low target IOP (10-12 mmHg) with minimal fluctuations. The patient was started on combination therapy (bimatoprost-timolol eye drops at 6 am in the morning and brinzolamide-brimonidine combination at 9 am and 9 pm twice daily in both eyes. The patient was asked to follow-up after 6 weeks. The patient developed a severe allergy to brinzolamide-brimonidine combination and stopped therapy on his own. The patient also could not afford long-term medical therapy and was counselled to get trabeculectomy done in both eyes. The patient was advised a 2 weeks course of topical steroids under cover of oral acetazolamide prior to trabeculectomy to decrease conjunctival inflammation.

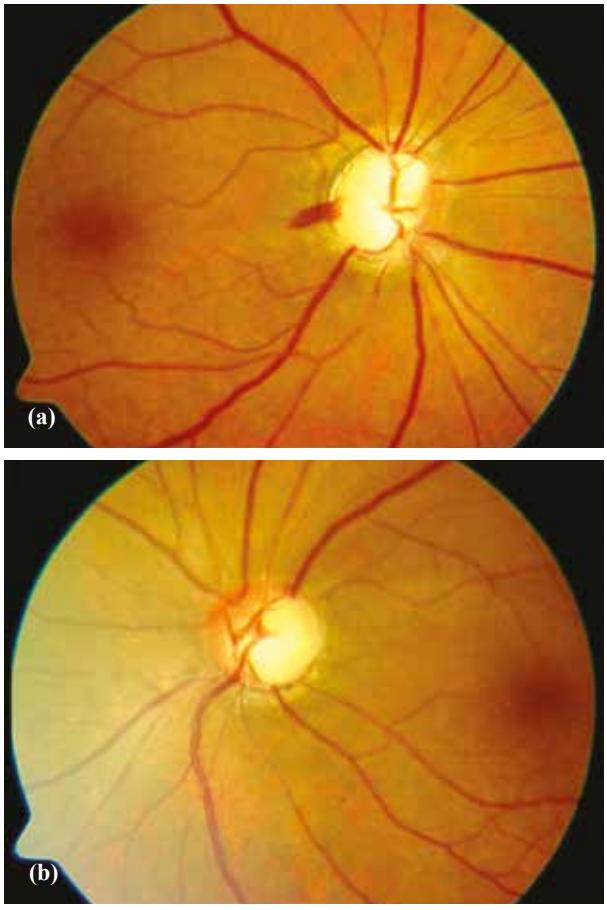
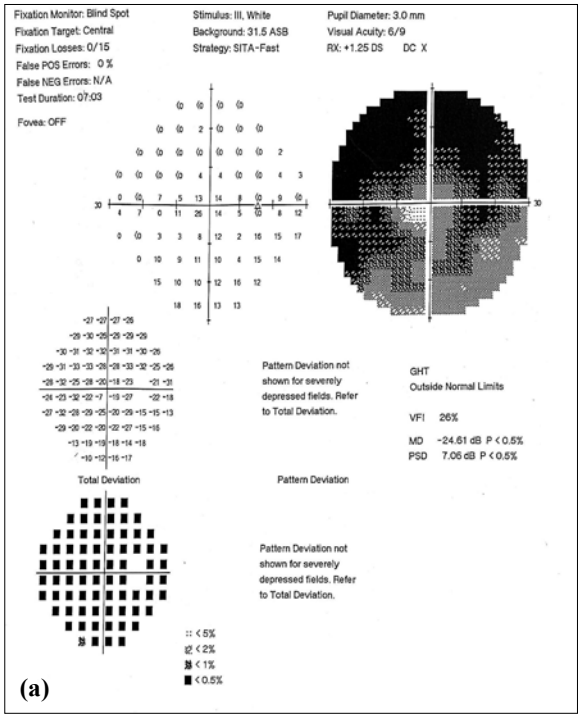


Figure CS5-1: Fundus picture of Right eye (a); Left eye (b)



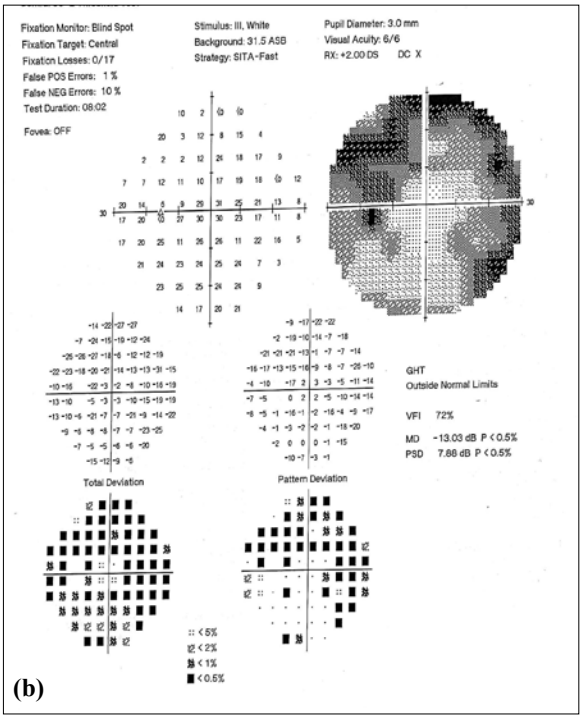
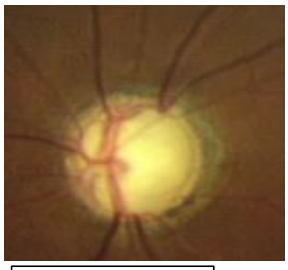


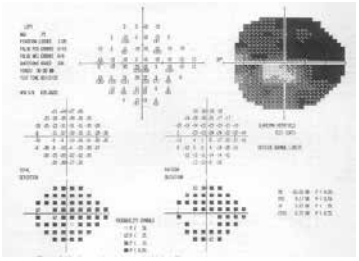
Figure CS5-2: Visual field of Right eye (a); Left eye (b)

Part - I: Management Algorithm for Advanced POAG



VCDR >0.85

Advanced POAG
VCDR >=0.9
Scotoma in both hemifield or within 10 degree of fixation
MD worse than -12dB



Scotoma in both hemifield, within 5 deg of fixation
MD less than -12dB

Note highest baseline IOP
Start medical therapy- First line Prostaglandins + beta blocker
Second Line: CAI/ Alpha agonist
Set target IOP (≤12 mmHg)
Check IOP at 2 weeks

Target IOP not reached and confirmed progression noted on RNFL OCT or Visual Field

Ensure compliance^
Add /Switch medication/ trial of SLT
Rule out other causes of progression$

Target IOP not reached on MTMT #

Trabeculectomy**
(with antimetabolites)

Target IOP reached

3 monthly Review

IOP
Structural tests (Disc Photo/OCT)
Visual Fields

HVF Progression noted (Consider 10-2; in addition to 24-2)

***Selective laser trabeculoplasty** can be added/ done at any stage.

****Indications of Trabeculectomy**

- IOP not controlled on maximum tolerable medical therapy (MTMT)
- Progression despite maximal medication
- Poor tolerance to medications
- Not able to afford medications
- Note: Look for Split fixation; Explain risk of "Wipe-Out"
  OCT Not of much use due to floor effect; Can't predict progression

$ **Other causes of progression**: steroid use, concurrent neurological disease, nocturnal hypotension, lifestyle changes.

^Ensure compliance by asking the number of bottles purchased, time of instillation, check technique of instillation

#MTMT= Maximum tolerable medical therapy

Part - J: Case Study: Glaucoma Progression

A 53-years-old female POAG patient was on follow-up for glaucoma for past 8 years. The vertical cup-disc ratio was 0.7 in the right eye with a small inferior NRR notch and 0.8 in left eye with a large inferior NRR notch (Figure CS6-1, 6-2). The baseline IOP was 20 and 24 mmHg in right and left eye with CCT of 488 and 490 µm in right and left eye respectively. There was a superior arcuate scotoma in both eyes (Figure CS6-3). The target IOP was set in mid-teens. She was put on a prostaglandin analogue in both eyes, along with a beta blocker. She was allergic to brimonidine and dorzolamide. Over time, the patient was irregular with medications and follow-up despite repeated counselling. IOP fluctuations due to improper use of medications was noted which ultimately lead to left eye glaucoma progression, while right eye did not progress (Figure CS6-4, 6-5).

The patient was counselled for surgery multiple times over the course of disease. Seeing patient reluctance for surgery, SLT was done in left eye. The IOP reduced to 12 mmHg on same medication for 3 months but rose again to 16 – 18 mHg after 6 months. Considering the risk of further progression the patient underwent left eye trabeculectomy and has maintained IOP between 10-12 mmHg over the last 1 year.

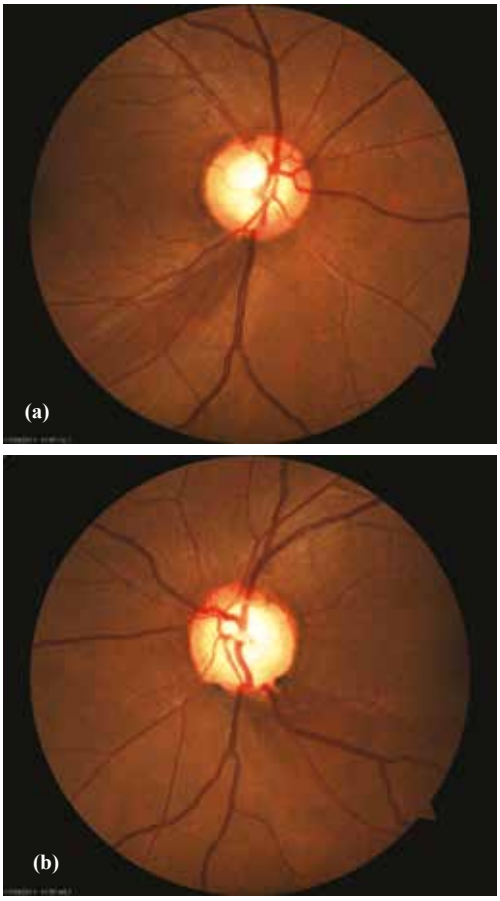


Figure CS6-1: Fundus picture of Right eye (a); Left eye (b) in 2011.

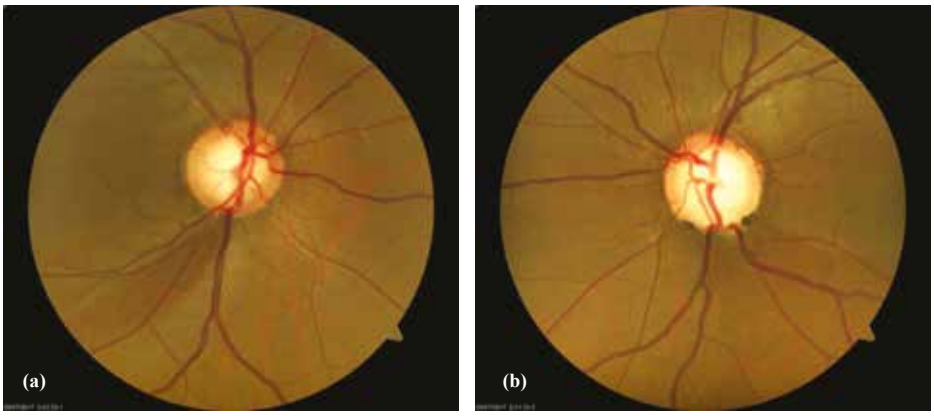


Figure CS6-2: Fundus picture of Right eye (a); Left eye (b) in 2018 showing enlargement of RNFL defect in left eye.

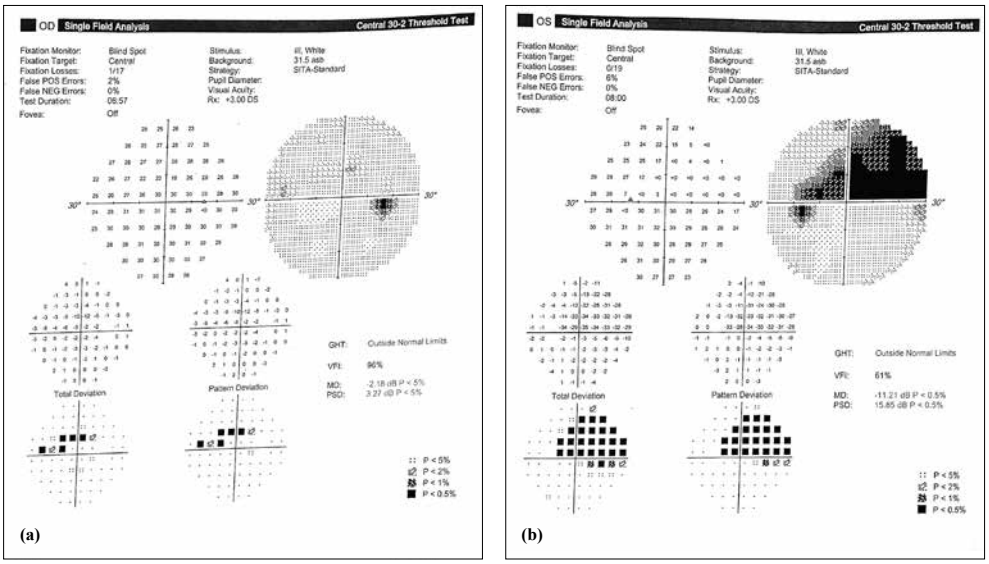


Figure CS6-3: Current Visual field of Right eye (a); Left eye (b)

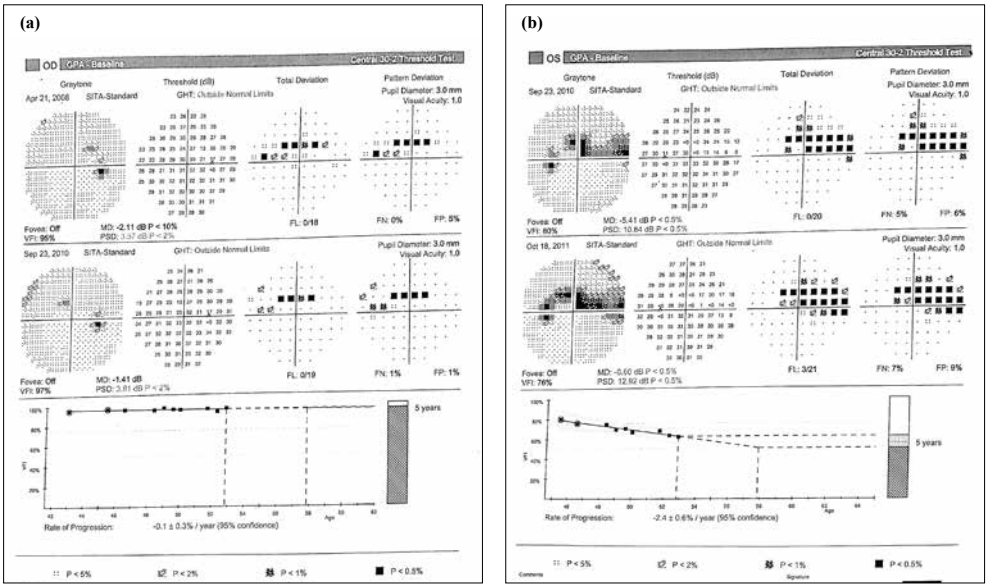
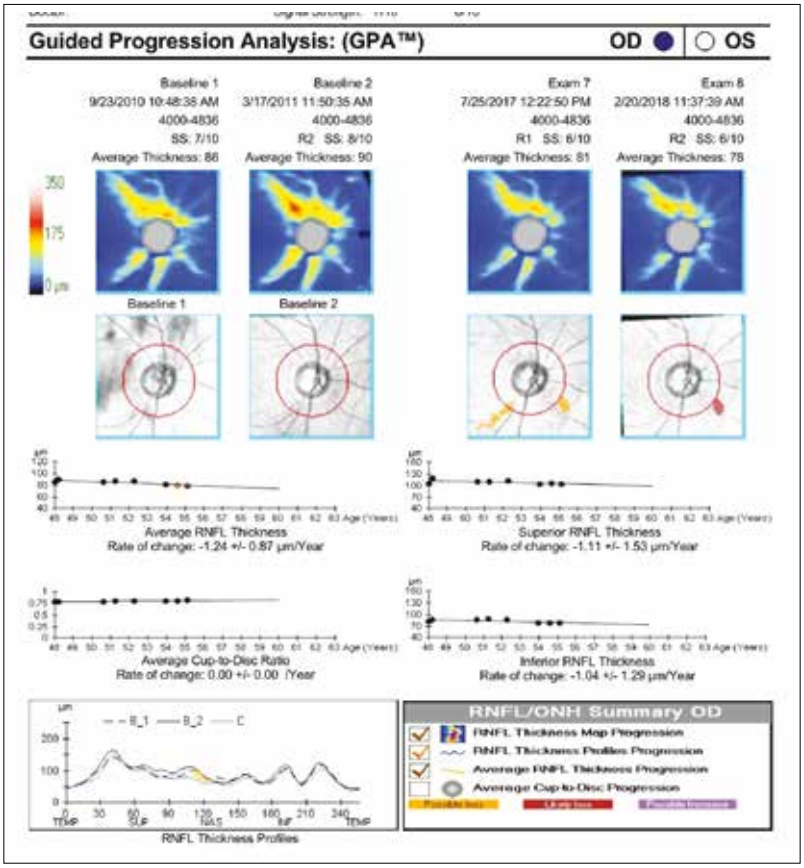


Figure CS6-4: Guided progression analysis visual field of Right eye (a); Left eye (b) showing significant progression in left eye.

(a)



(b)

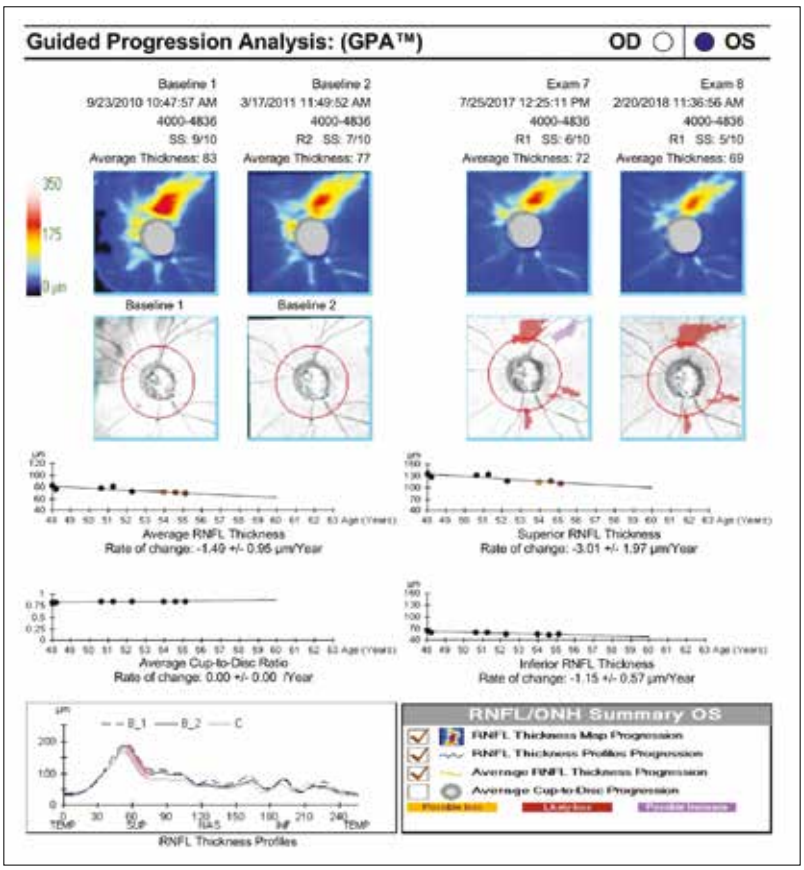


Figure CS6-5: Guided progression analysis RNFL OCT of Right eye (a); Left eye (b).

Part - K: Case Study: Normal Tension Glaucoma

A Thirty-six-year-old lady presented for examination & further evaluator after being diagnosed with glaucoma elsewhere. She was being treated for diabetes and hypertension. Her best corrected visual acuity was 6/6 and N6 OU. Anterior segment evaluation was normal OU. Gonioscopy revealed open angles OU. Diurnal IOP OD was 12 to 18 mmHg and 12 to 20 mmHg OS. Central corneal thickness was 521 OD and 528 microns OS. Optic nerve head appearance and visual field examination reports are depicted in Figures CS7-1 and CS7-2. She was initially started on Brimonidine 0.1% twice-a-day but developed an allergic reaction after which the drug was substituted by Latanoprost 0.005% at bed time. She was followed up from 2005 to 2017. She developed recurrent disc hemorrhages especially in her left eye (Figure CS7-3). She also showed progressive visual field loss in her left eye (Figure CS7-4) despite good adherence to medical treatment which was stepped up to reach lower target IOP as required. Her compliance with treatment of diabetes was poor and her anti-hypertensive treatment had to be stepped up thrice.

She underwent carotid and vertebral artery Doppler imaging which revealed diffuse intimal thickening but no stenosis. She then underwent color Doppler imaging which showed reduced blood flow in the left posterior vessels (Figure CS7-5).

In summary, this was a female patient with systemic vascular disease who presented with IOP in the normal range and recurrent disc hemorrhages. Progressive visual field loss occurred in her left eye despite appropriate treatment and adherence to treatment. Further investigation revealed reduced blood flow parameters in her left eye which could have contributed to her visual field progression. The patient was counselled to get trabeculectomy done in her left eye.

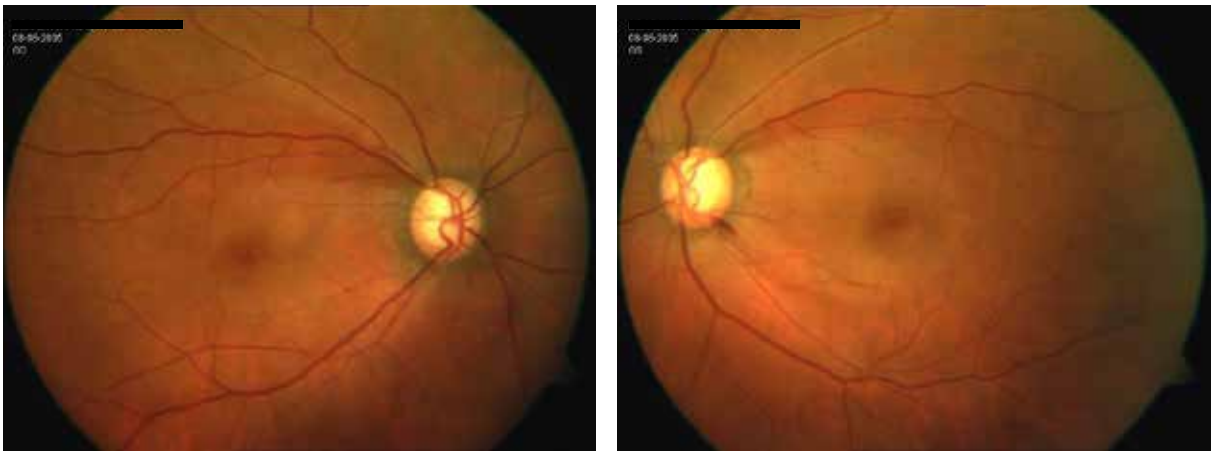


Figure CS7-1: Optic nerve head at presentation

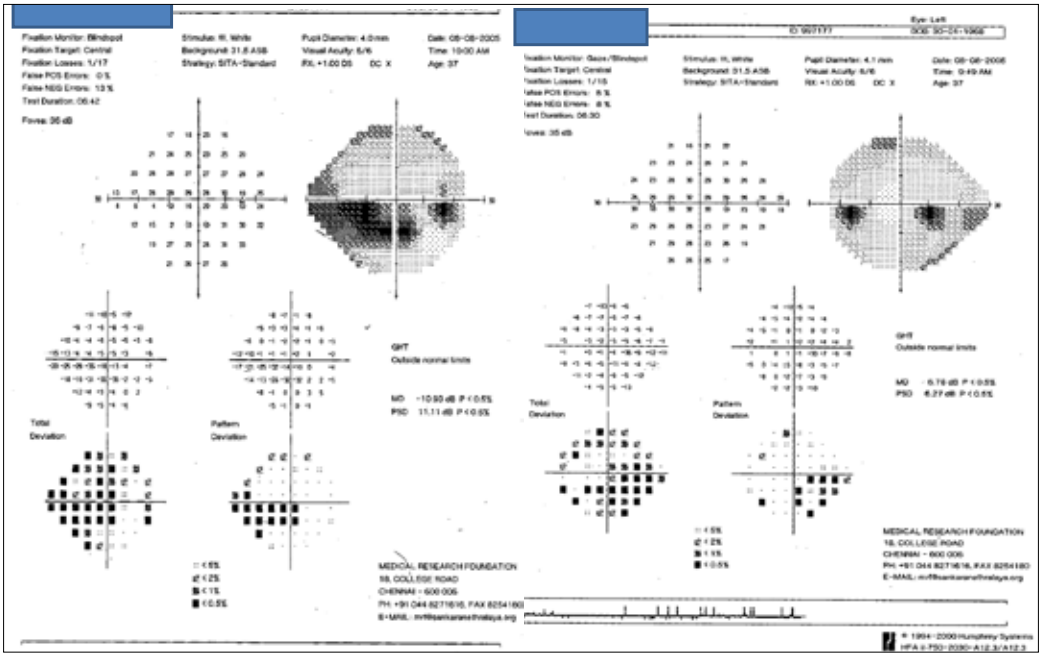


Figure CS7-2: HVF 24-2 SITA standard

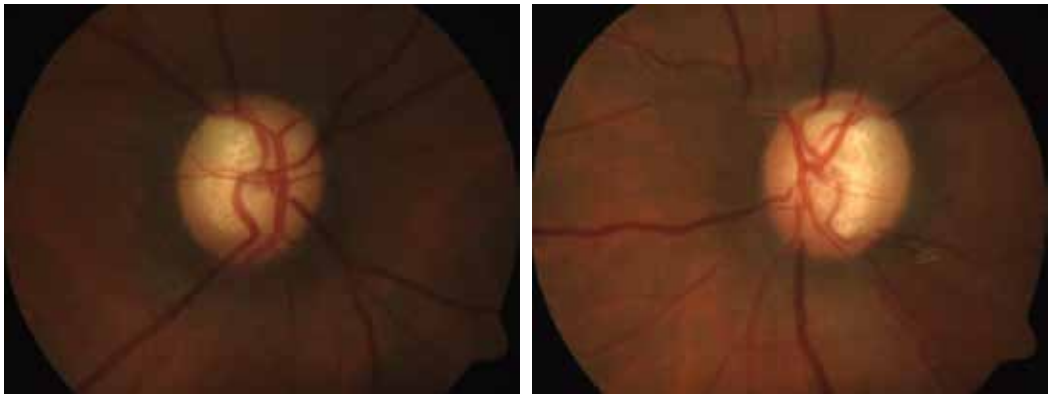


Figure CS7-3: Optic disc appearance in 2017

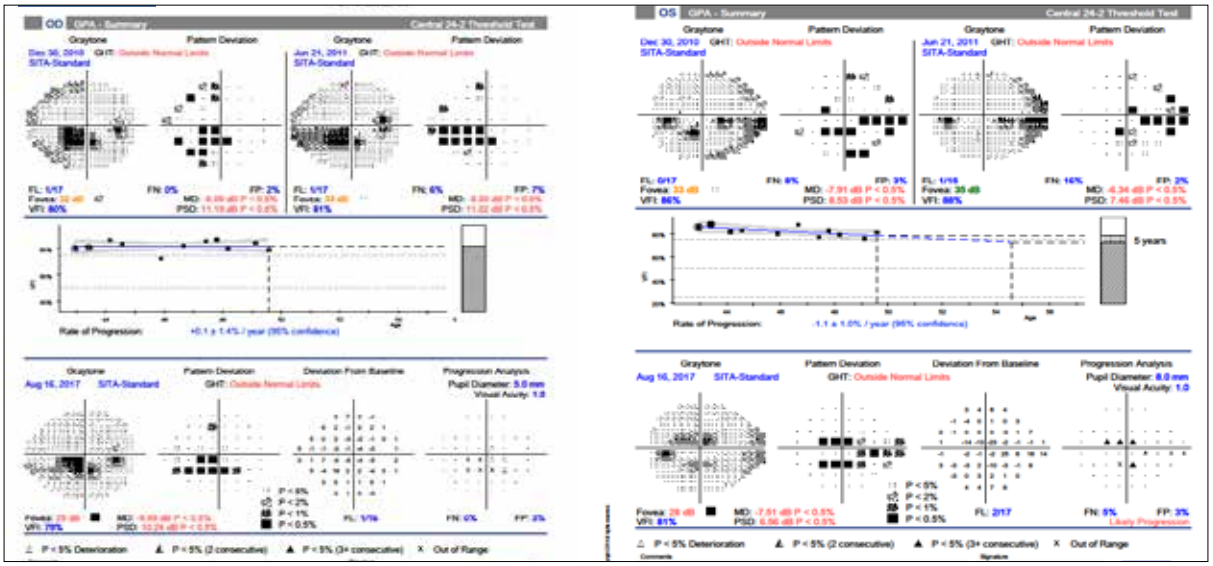


Figure CS7-4: Guided progression analysis

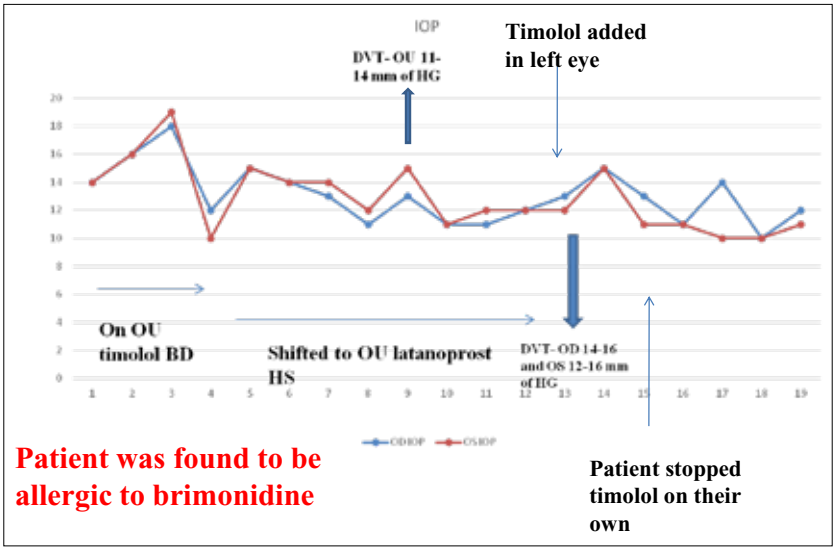
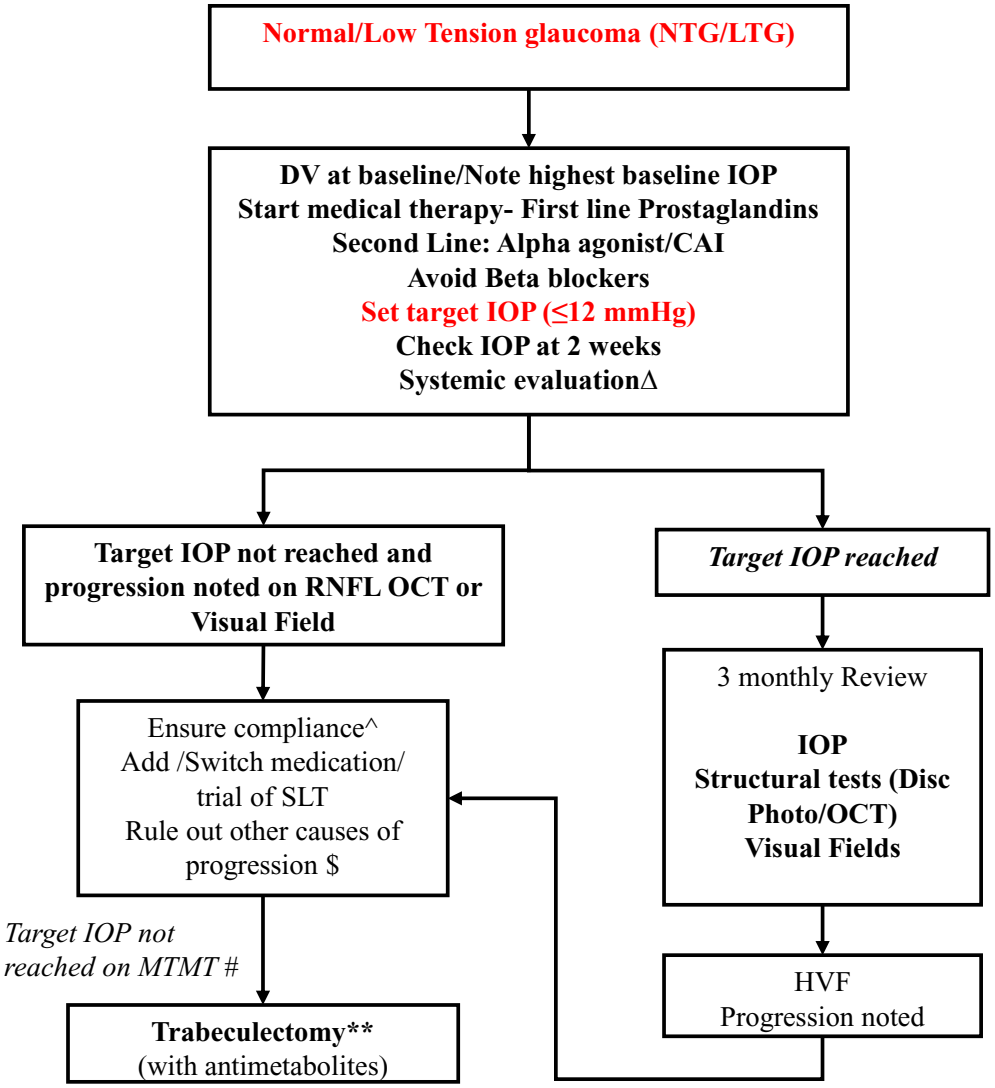


Figure CS7-5: Summary of IOP at each visit

		Right eye	Left eye	Normal value
Ophthalmic artery	PSV	7.2	11.4	42.2
	EDV	1.6	2.8	10.5
	RI	0.7	0.9	0.7
Retinal artery	PSV	8.4	7.5	13.4
	EDV	2.0	1.2	3.6
	RI	0.76	0.8	0.7
Short posterior ciliary artery	PSV	8.7	3.0	10.7
	EDV	4.0	0.9	3.5
	RI	0.7	0.7	0.6

Figure CS7-6: Colour Doppler imaging: Ocular blood flow analysis

Part - L: Management Algorithm for NTG



***Selective laser trabeculoplasty** can be added/ done at any stage.

****Indications of Trabeculectomy**

- IOP not controlled on maximum tolerable medical therapy (MTMT)
- Progression despite maximal medication
- Poor tolerance to medications
- Not able to afford medications

^Ensure compliance by asking the number of bottles purchased, time of instillation, check technique of instillation

$ **Other causes of progression**: steroid use, concurrent neurological disease, nocturnal hypotension, lifestyle changes.

ΔSystemic evaluation

- Blood pressure diurnal
- Sleep Apnoea
- Carotid Doppler

#MTMT= Maximum tolerable medical therapy

Part - M: Case Study: Pigment Dispersion Syndrome

A 22-year-old male student was referred as a case of non-resolving uveitis with high IOP for 1 month. He was on topical low-potency steroids and cycloplegics. He was also taking brimonidine and timolol combination medication twice daily and capsule acetazolamide sustained release 250 mg twice daily. His IOP was 24 mmHg in right eye and 20 mmHg in left eye.

On examination, he had pigments over the corneal endothelium in the form of a vertical column (Krukenberg spindle), no keratic precipitates were appreciated. The anterior chamber was abnormally deep and few pigments were seen floating in the angle. Gonioscopy revealed a dark band of pigmentation over the trabecular meshwork in superior and inferior angles of both eyes (Figure CS8-1, 8-3). The cup-disc ratio in both eyes was 0.4 and visual fields were normal (Figure CS 8-2).

A diagnosis of Pigment Dispersion syndrome (PDS) was made and the cycloplegics and steroids were stopped. Glaucoma drugs were continued and tapered with time. YAG iridotomy was done in both eyes to reduce reverse pupillary block.

Pigment dispersion syndrome needs to be differentiated from uveitis for appropriate management and keratic precipitates should be distinguished from pigment. Sudden release of pigment on dilatation suggest active pigment dispersion and the patient can benefit from laser iridotomy.

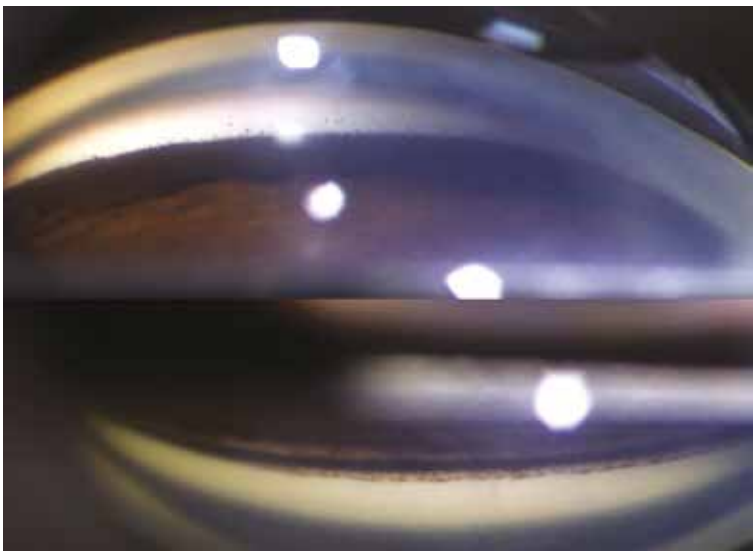


Figure CS8-1: Gonioscopy picture of upper and lower angle.

Figure CS8-2: Fundus picture of right and left eye

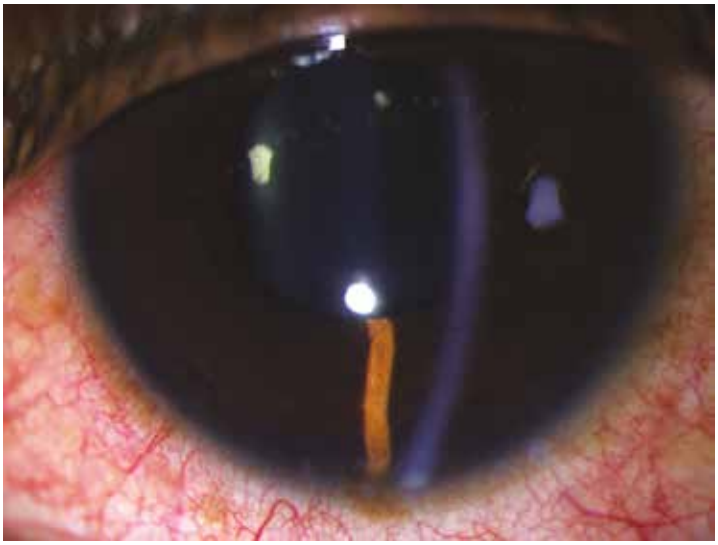


Figure CS8-3: Iris configuration showing posterior bowing of iris

Annexure - I

OPTIC DISC MODULE

Part - A

Glaucomatous Optic Neuropathy

1 Introduction

Glaucomatous optic neuropathy is defined by changes in the optic nerve head. While elevated intraocular pressure (IOP) is an important risk factor,[1,2] IOP measurement is not reliable for glaucoma diagnosis.[3] Often examination of the optic disc leads to the first suspicion and many times confirmation of the glaucomatous neuropathy. Morphology of the optic nerve head varies greatly in normal as well as in eyes with glaucoma, therefore considerable skill is required to evaluate optic discs for glaucoma.[4] From our experience with the online GONE (glaucomatous optic neuropathy evaluation) project we found that optic disc evaluation is a clinical skill that can be learned with practice. The purpose of this book is to help develop/refine those skills. This book is supplemented by an online resource 'The GONE project, www.gone-project.com' which is a good tool for learning as well as testing optic disc evaluation skills for glaucoma.

Traditionally, there are a number of parameters that need to be considered while evaluating optic discs for glaucoma.[5] These parameters include disc size, disc shape, cup-to-disc ratio (CDR), configuration of neuro-retinal rim (NRR), presence of disc hemorrhages, retinal nerve fiber layer (RNFL) defects and Peripapillary atrophy (PPA). Each one of these parameters is important in defining the three dimensional structure of the ONH. They can vary greatly in health and disease and influence how normal and abnormal nerves are distinguished. Keeping account of all the parameters and synthesizing them in to a clinical diagnosis can be a daunting task which requires a systematic approach to optic disc evaluation.

The 4-3-2-1 System

There are a number of ways to examine the disc systematically,[6,7,8] but all are aimed at the same task: to encourage a methodical approach and to recognize and capture features of the nerve head that confers greater risk of glaucoma than others. Many are lists of likely pathological changes, or are aimed at pattern recognition. Such approaches have variable levels of sensitivity and specificity for glaucomatous optic neuropathy.

Many previous methodological approaches lack emphasis on the basic anatomy of the disc. Data from our GONE study found that many of the errors made by novice optic nerve observers had their root in not understanding the basic anatomy of the disc – before any pathological process had occurred. For instance a CDR of 0.50 can be normal in the setting of a large disc but abnormal in the setting of a small disc. Discs that are tilted intrinsically have an abnormal appearance and interpreting glaucomatous changes in these discs are more difficult. The variations of the ONH are such that some normal variants can look abnormal, and some that could pass for normal are not.

The 4-3-2-1 disc examination system was developed with the aim of first looking deliberately at the underlying structure, and then at the neuroretinal tissue changes. The underlying structural issues relate to the scleral canal and lamina cribrosa. We first look at the scleral canal: its shape, size and orientation, and the peri-papillary atrophy. These 4 are the "outside" features.

The neuronal and glial assessment is mostly captured in the rim shape and thickness. Along with cup depth (mostly associated with the position of the lamina cribrosa) make up the 3 "inside" features.

Changes in the retinal nerve fibre layer and disc rim haemorrhages are very useful findings, and we use these 2 findings as confirmation.

Then finally we need to put it all together – synthesizing the examination data into a risk and severity or glaucoma likelihood. This is the most important step in directing management decisions in clinic.

Thus, there are ten facets to the examination in all:

4.4	Peri-Papillary Atrophy (PPA)	**"Outside"**
4.3	Disc (scleral canal) size	
4.2	Disc shape	
4.1	Disc tilt	
3.3	Cup Depth	**"Inside"**
3.2	Cup Rim	
3.1	Cup-to-Disc Ratio (CDR)	
2.2	Retinal Nerve Fibre Layer (RNFL)	**"Confirmation"**
2.1	Disc Rim Haemorrhage (Hmge)	
1.0	Glaucoma?	**"Synthesis"**

In the subsequent pages we will describe the optic disc evaluation based on the above schema, with plenty of illustrations. Readers are encouraged to try the online resource "The GONE project" for further learning and assessment of their disc evaluation skills. You can find more details about the GONE project in Chapter 5.

References

1. Musch DC, Gillespie BW, Niziol LM, et al, CIGTS Study Group. Intraocular pressure control and long-term visual field loss in the Collaborative Initial Glaucoma Treatment Study. Ophthalmology 2011;118:1766–73.
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3. Realini T, Weinreb RN, Hobbs G. Correlation of intraocular pressure measured with goldmann and dynamic contour tonometry in normal and glaucomatous eyes. J Glaucoma. 2009;18(2):119-23.
4. Jampel HD, Friedman D, Quigley H, Vitale S, Miller R, Knezevich F et al. Agreement among glaucoma specialists in assessing progressive disc changes from photographs in open-angle glaucoma patients. Am J Ophthalmol 2009;147:39–44.
5. Fingeret M, Medeiros FA, Susanna Jr R, Weinreb RN. Five rules to evaluate the optic disc and retinal nerve fiber layer for glaucoma. Optometry 2005;76:661-8.

2 The "Outside"

This section is directed to the examination of the scleral canal: its correct identification and delineation. From our analysis of results from the GONE project, incorrect assessment of the outer limit of the optic disc is one of the most common mistakes made by ophthalmology trainees.[1] Incorrect assessment of the outer limit will lead to errors in assessing neuroretinal rim and thus have profound influence in over or underestimating the likelihood of glaucoma.[2] The systematic analysis of the "Outside" (illustrated in Figure 1) starts with the demarcation of the PPA. The outer limits of the PPA can be abrupt or merge with retinal pigment epithelium (RPE) changes (known as zone alpha) and the inner limit is the scleral ring, where no RPE is present normally. Then the scleral ring is identified giving both the size and shape of the scleral canal. Finally, the orientation of the canal (disc tilt) is assessed as an oblique entry produces certain characteristic appearances that can mimic or disguise glaucoma.

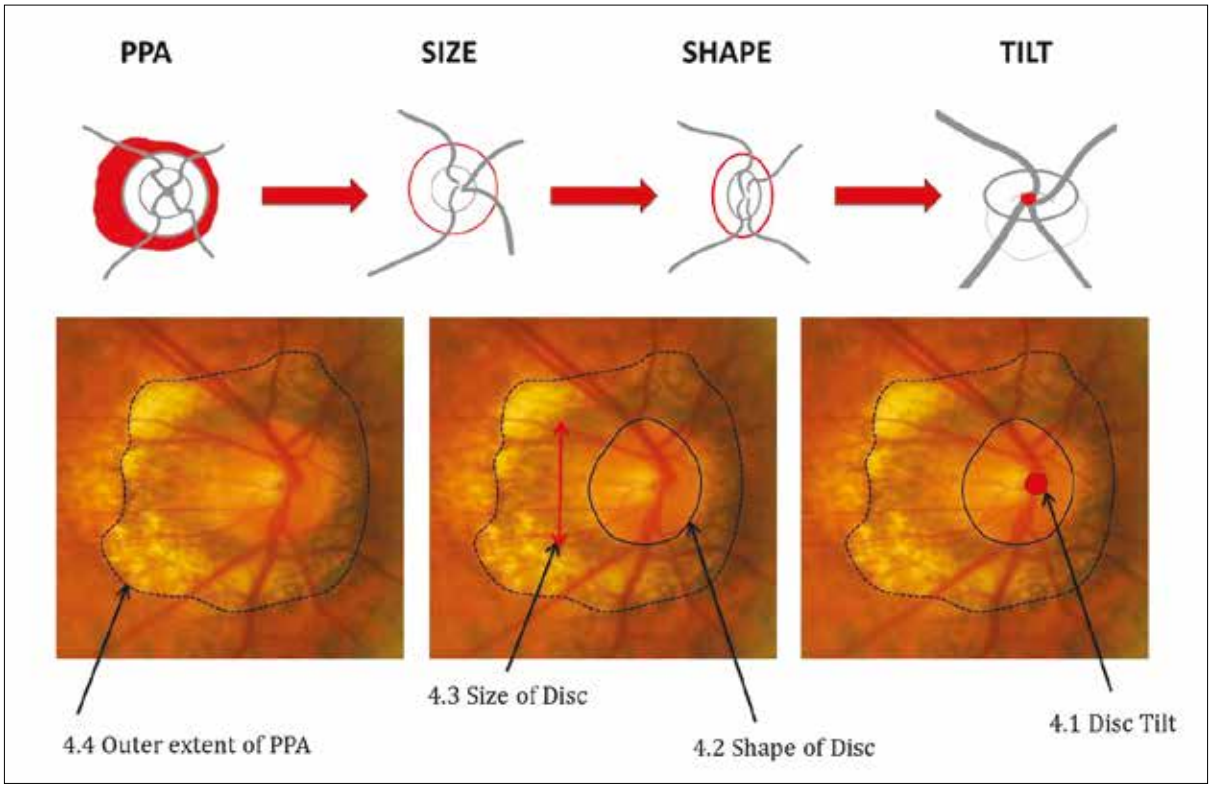


Figure 1

4.4 Peripapillary Atrophy (PPA)

a. What is peripapillary atrophy?

Peripapillary Atrophy (PPA) is the area of pigment change contiguous with the disc margin. It varies in appearance from irregular changes in pigment/RPE (zone alpha), to total loss of pigment/RPE with visible choroid (zone Beta), to the scleral pallor of myopic degeneration and scleral crescents where there is loss of

pigment/RPE and the underlying choroid (although this zone is often differentiated from true PPA as there is no choroid).

True PPA is divided in two zones: alpha and beta. Zone beta and myopic/scleral crescents have the most importance for the assessment of optic disc.[3]

Myopic degeneration or scleral crescents are pale and have no choroid beneath the RNFL. They exist mostly where there is high myopia or where there is marked tilting of the disc. They can confuse the examiner as to the exact margins of the disc. There is total loss of photoreceptors over the area of degeneration and therefore produces an absolute scotoma – enlarged blind spot.

Zone beta PPA is where the choroid overlays the sclera, although there is a complete absence of the RPE and photoreceptors. Choroidal vasculature may be visible. This is an area of complete scotoma – enlarged blind spot.[3]

Farthest away from the disc margin is the area of zone alpha PPA. It is of limited clinical significance. It is an area of RPE change and associated photoreceptor dysfunction. This is an area of little change or relative scotoma.[3]

The junction between zone beta and zone alpha may not be clear, but this is rarely of any significance. The most important part of PPA is recognizing its existence, watching for asymmetry, and being clear on its effect on determination of scleral canal margin.

b. How is it measured?

PPA can be measured either on photograph or on OCT, particularly later generation Spectral-Domain OCTs with greater penetration.[4] Actual measurement of PPA is of less value, although it is important to recognize where it is quite asymmetric, and sometimes it is in an area where the neuroretinal rim is deficient.

The determination of the junction between the scleral canal and the PPA needs be accurate. Recognizing the disc margin where the disc and PPA are an eccentric shape can take practice.

c. PPA - Why is it important?

The development and extent of PPA is associated with glaucoma. Glaucomatous optic neuropathy can produces an increase in PPA. Although PPA does occur in normal eyes and other disc pathology (15-20%) both alpha and beta PPA are more common in glaucoma (70%). When examining the ONH, PPA can confuse the observer into underestimating the risk by overestimating the scleral canal size. On a cursory look, PPA can be mistaken for neuro-retinal rim (NRR) and allow the examiner to believe that the NRR rim is wider than it really is.

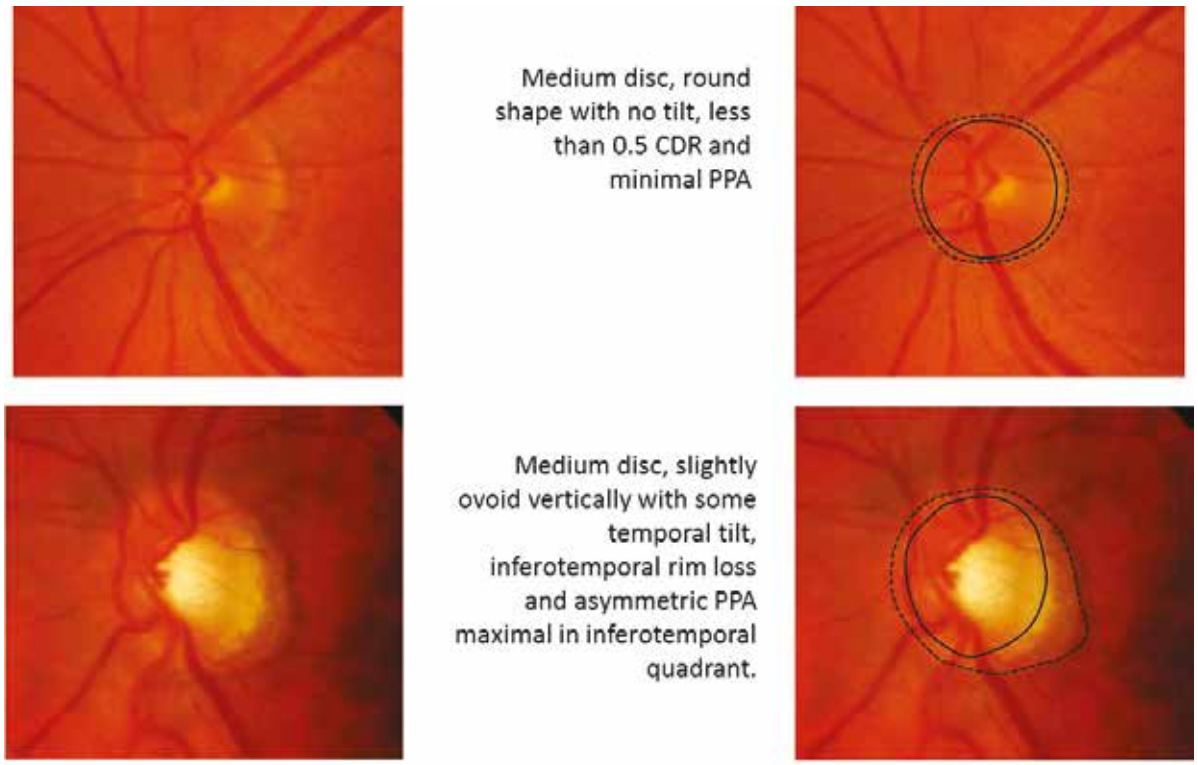
Identifying what is PPA and where the exact markings of the scleral canal are, is critical to accurate assessments of disc health. Mistaking PPA is most likely to cause problems with disc size, and disc size is most likely to cause problems in underestimating both the diagnosis and severity of glaucoma on disc examination. In our GONE project study, we found ophthalmology trainees are more likely to underestimate the glaucoma risks of optic nerves with moderate PPA, likely because insufficient care was taken to identify the PPA and thus resulting in incorrectly thinking the area of PPA is NRR.[1]

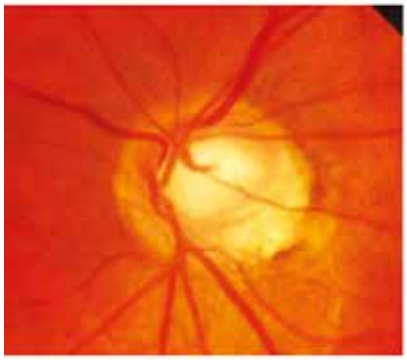
d. Background information

Normally there is a gradual increase in peripapillary atrophy with age. Greater PPA has been associated with glaucoma and glaucoma progression. It is more frequently found in glaucoma (>70%) than in normal or other disc pathology (<20%). It is also associated with quadrant of the disc with maximal neuroretinal loss. Cross-sectional studies also show the site of PPA can be associated with the site of disc haemorrhage.[5] However PPA is less associated with disc damage in angle closure glaucoma.

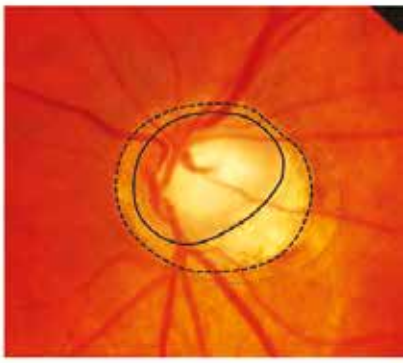
PPA is different from myopic and scleral crescents which are not strongly associated with glaucoma. However all changes in the tissue that surrounds the scleral canal can make it more difficult to ascertain the disc margins, and hence can contribute to errors in correct demarcation of the "outside" of the disc.

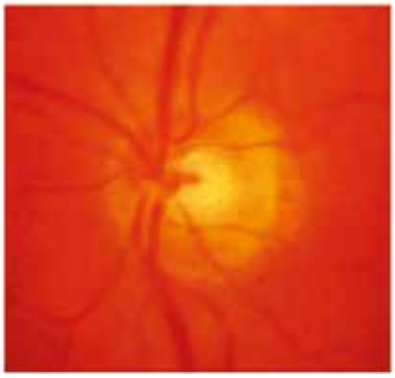
e. Examples



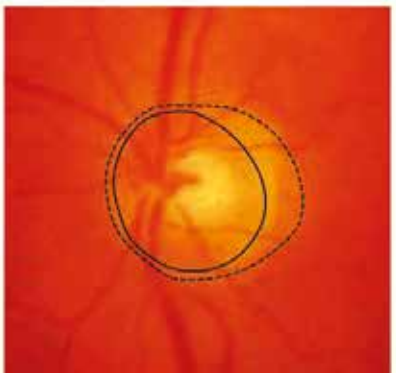


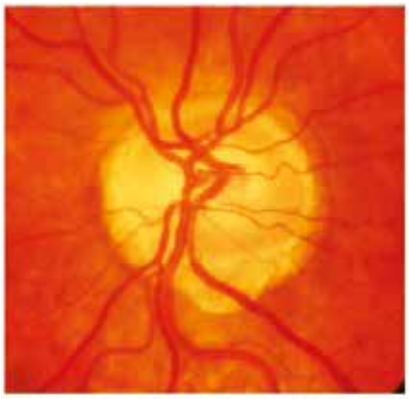
Medium disc, ovoid horizontally (some rotation) with some supero-temporal tilt, inferotemporal rim loss and asymmetric PPA maximal in inferotemporal quadrant. (Area of zone alpha marked in dotted line).



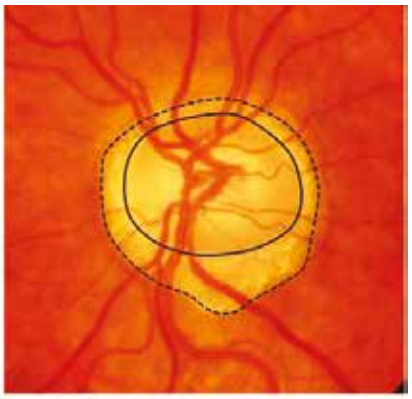


Medium disc, mildly ovoid vertically. Indistinct margins of disc and PPA (marking may include some zone alpha temporally).

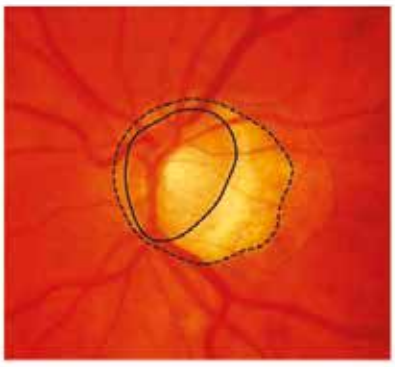


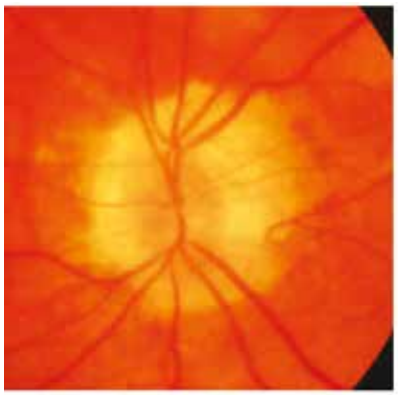


Large disc, ovoid horizontally. Moderate PPA, more inferiorly. Zone alpha marked in dotted line.

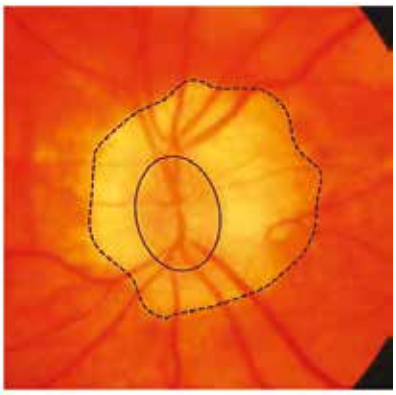


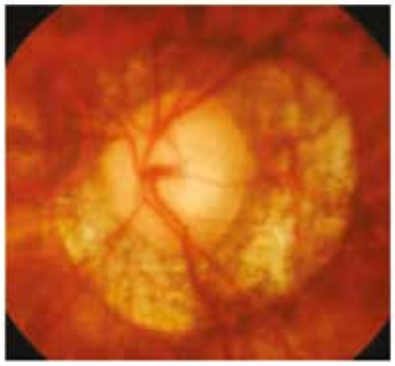
Small to medium disc, ovoid vertically (some rotation) with temporal tilt, inferotemporal rim loss and asymmetric PPA maximal in inferotemporal quadrant. (Area of zone alpha marked in dotted line).



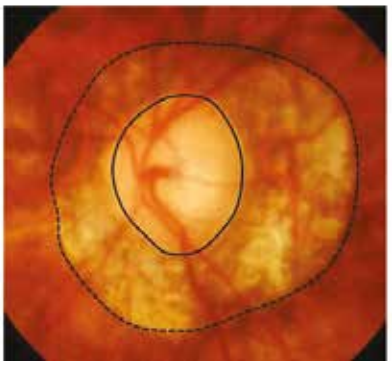


Small disc, ovoid vertically with no tilt or rotation, extensive PPA. Note the shallow cup and extensive PPA in this case makes the outer disc margin indistinct.





Medium to large disc, ovoid vertically with no tilt or rotation, 0.8+CDR, extensive PPA.



4.3 Disc Size

a. What is the parameter disc size?

Discs, or more precisely the anterior end of the posterior scleral canal, normally vary considerably in size. Disc size varies from quite small, around 0.8 mm^2, which is a hypoplastic disc, to around 6.0 mm^2, which is a macrodisc (often myopic). The size and shape of the disc are key features in understanding the structure of the optic nerve head. Identifying the scleral canal requires discerning the boundary between the neuro-retinal rim tissue and the scleral (scleral ring), exposed choroid (zone beta PPA) or RPE and overlying nerve fibre layer.

The disc size is the measurement or estimate of the dimensions of the internal or front end of the scleral canal. This is the visible portion of the scleral opening and is measured horizontally and vertically.

A more accurate calculation of disc size may be expressed as surface area, rather than dimensions. This is usually calculated by machine, although such a calculation will assume a near circular regular shape a condition which may not be the case.

Ocular Coherence Tomography (OCT), particularly those with greater tissue penetration, can sometimes pick up the scleral canal quite well, but more reflectance machines such as GDX and earlier OCTs will tend not to.

b. How is it measured?

The disc is measured as though it was a two-dimensional structure based on its vertical and horizontal dimensions. Many discs are close to round or ovoid vertically, although some have somewhat asymmetric shapes.

When we measure the disc, we are measuring the anterior end of the scleral canal. Sometimes this is more visible than others and some parts of the disc may be more visible than others.

The scleral canal can be shaped somewhat as a funnel and may be angled with respect to the posterior scleral surface (tilt). Detecting the margins of a markedly tilted or oblique inserting nerve can be particularly challenging. Indeed in our GONE study, we found discs that are tilted are much more likely to have overestimation of glaucoma risk than normal discs.[2]

In order to measure disc size, the margins of the scleral canal needs to be accurately determined. One area of confusion is the determination of the junction between PPA and optic nerve edge. As discussed in 4.4, PPA and scleral crescents can confuse the examiner into assigning the disc margin incorrectly.

The most compelling evidence for the position of the disc margin will be a color change: the scleral canal margin usually being a pale ring forming the external border to the darker (more red) end on view of the axons and glia of the retinal nerve fibre layer as it bends to enter the scleral canal (the "neuro-retinal rim", NRR). There may also be a change in contour at this point, but only if the rim is almost non-existent. The colour change occurs due to the change in vascularization. The disc margin is more obvious with deeper cup, as the volume (or end on depth) of NRR is greater with a deeper cup. For this reason, if the lamina and the sclera lie on the same plane (such as in high myopia and shallow cupping) then the differentiation of the disc margin can be more difficult. The disc rim also becomes more difficult to discern where the disc is smaller and the axonal/glial mass is crowded and heaped up.

c. Why is it important?

Establishing the correct disc margins, and hence disc size is one of the most important determinants in establishing whether the NRR is healthy and appropriate in dimensions.

The scleral canal is where neural axons pass through to form the optic nerve. If two eyes have the same amount of axons passing through the canal, the eye with a small optic disc will appear to be more crowded and has a smaller CDR compared to a larger disc with more space for axons to pass through. Therefore the assessment of neuroretinal rim must take into account the size of the ONH.

Errors that occur for incorrect disc size can significantly alter the interpretation of the nerve. Although there are many associations to incorrect disc size estimation, not correctly identifying the scleral canal margins is the most important identifiable error that we recognized from the GONE data.[1]

Eyes with large discs were found to be more likely to have overestimation of glaucoma risk by ophthalmology trainees.[2] This is because large discs often have intrinsically larger cup:disc ratio despite having healthy NRR, which can cause confusion to the inexperienced observer. On the other hand, over-estimating disc size because of incorrectly identifying scleral canal margin tends to create an error of undercalling the disc risk, thus potentially missing the pathological changes of glaucoma. It can be difficult to identify exactly where the margins of the scleral canal are, and certain disc anatomy makes this more complicated. Tilting, high myopia, significant PPA, and a relatively pale fundus are reasons why it can be more difficult.[6] In addition, shallow cupping can also make the margins less clear.

It is rare to incorrectly assign a scleral rim size smaller than actual. The most common error is to assign one too large, which then necessarily makes the NRR appear thicker than it is.

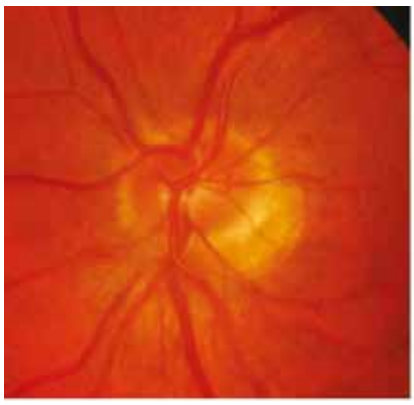
d. Background information

The optic disc size is fixed in late childhood in the absence of ocular pathology (high myopia or glaucoma), is relatively independent of refractive error from -5 to +5 D, gender and body size. Disc size is influenced by race (which seems to follow skin pigmentation – with Africans having statistically the largest discs), and refractive error greater than -5 or +5 D.

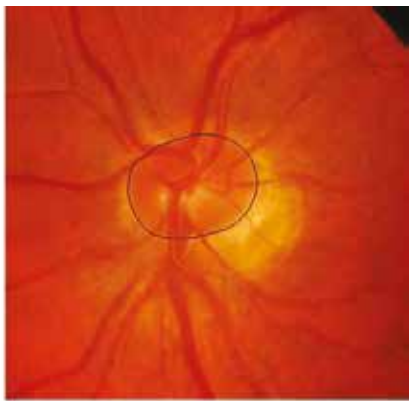
On an average, larger discs are found in myopes>5D and smaller discs found in hypermetropes>5D. Disc size and shape are inherited.[7]

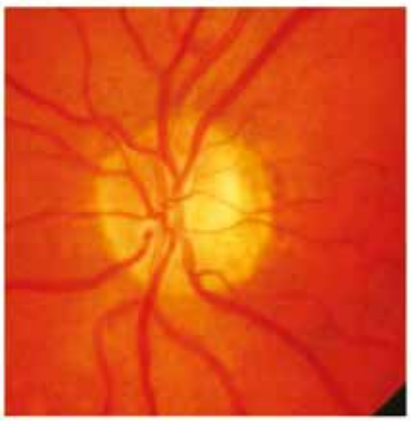
Disc size can be classified into small, medium and large. Larger discs have more lamina pores and more neurons, and more photoreceptors. Smaller discs have a greater risk of drusen, pseudopapilloedema and non-arteritic anterior ischaemic optic neuropathy (NAION).

e. Examples

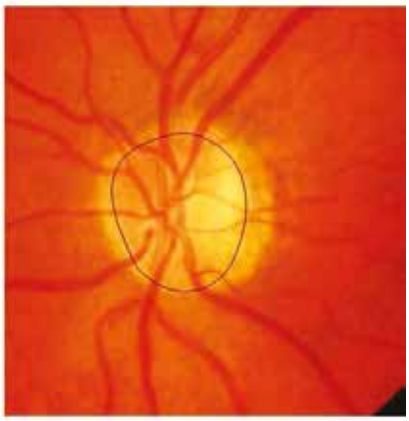


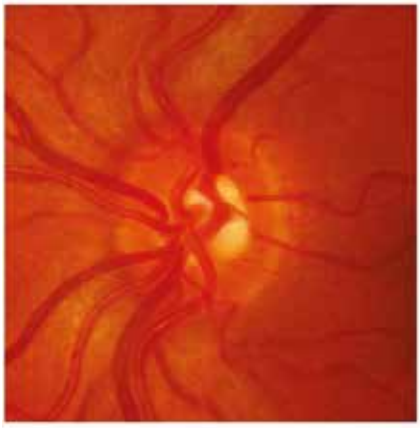
Very small disc – hypoplastic
This disc is also ovoid horizontally and tilted vertically with asymmetric PPA.
As is common it has a small and shallow cup.



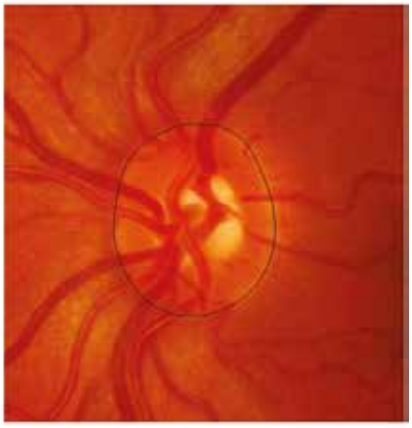


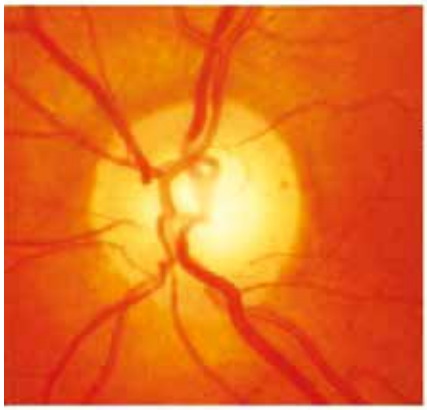
Small disc.
This disc is also ovoid vertically with asymmetric PPA. The margins of the disc are less clear as the disc is a little 'crowded' with partial obscuration the scleral margin.
As is common it has a small and shallow cup.



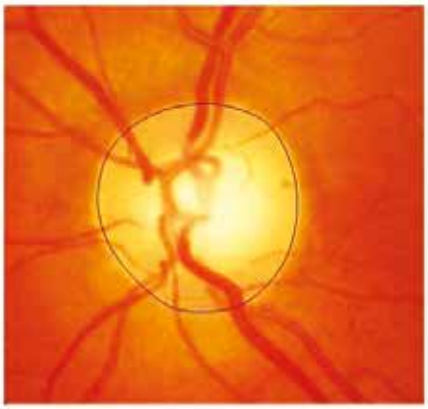


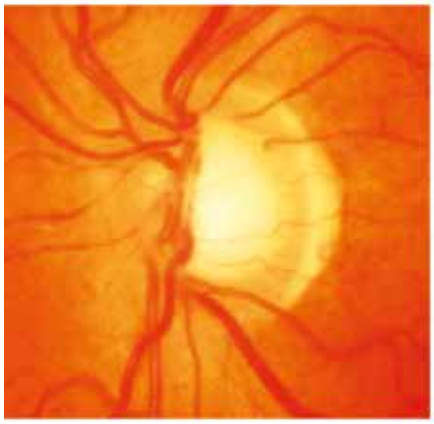
Medium sized disc.
This disc has well demarcated margins and a deep cup. The veins look relatively prominent but this is likely to be a normal variant.
There is mild nasal tilting of the disc.



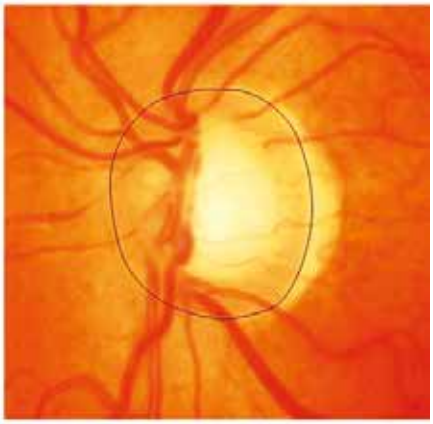


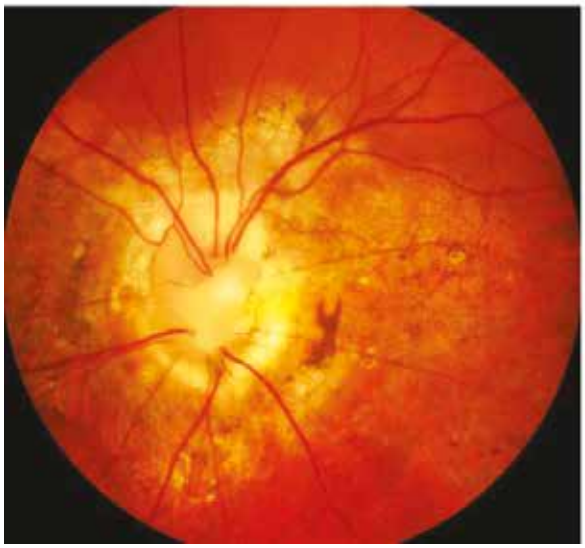
Large sized disc.
The temporal external margins of the disc are relatively clear – the nasal less so as the disc is tilted temporally. There is corresponding asymmetric PPA temporally. (least nasally). It is larger vertically than horizontally which is normal with a larger cup.





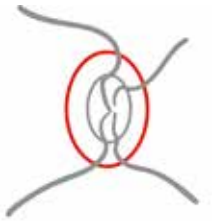
Very large sized disc.
The external margins of the disc are relatively clear (least inferonasally). It is not as regular in shape as smaller discs but is larger vertically than horizontally which is normal.
It has a relatively shallow cup, which makes clear definition of the inner rim less precise.





The Morning Glory Syndrome (rare) – with the usual pale centre and spreading of the disc structures. There is vascular branching out of view and marked PPA with blurred disc margins.

4.2 Disc Shape



a. What is disc shape?

Disc shape describes the shape of the anterior scleral opening: the internal end of the posterior scleral canal (that opening that allows optic nerve axons to exit the eye).

Most scleral canals have an (mildly) ovoid vertical shape, but there is variation. On average there is less variation in shape than that observed in disc size, but significant variation exists.

Ovoid discs are described in terms of their long axis – vertical ovoid means the long axis is vertical. Most ovoid discs are vertical or horizontal – discs that fall between these are oblique.

The shape of the disc can be disguised by the PPA (see section 4.4). The shape is defined by the scleral canal margins which requires careful delineation.

b. How is it measured?

Disc shape is measured by observation. It is not well delineated by machine. Most machines will perform a version of 'best fit' which will tend to regularize the shape.

Accurately describing the disc shape requires differentiating the scleral margin from the surrounding tissue. As described in 4.4 (PPA) and 4.3 (Size) determining the external margins of the disc is one of the key skills for successful analysis of the ONH. The examiner must be prepared to find a disc margin which does not assume a vertically ovoid shape. Although most ONH are shaped so that horizontal dimension is between 5% and 20% smaller than the vertical, those that do not fit this schema are much more likely to be inaccurately assessed.

Markedly ovoid discs may also be tilted (see 4.1). Because of the difference in visibility of the rim in these discs, particular care must be taken to discern the disc margin.

c. Why is it important?

Disc shape determines cup shape and therefore determines our ability to interpret the health of the neuroretinal rim. It is a common error to assume the disc shape is more regular, perhaps more round, than it really is. Getting this wrong inevitably leads to problems in neuroretinal rim assessment.

The ISNT Rule (which stands for Inferior, Superior, Nasal and Temporal in descending order of NRR thickness) is a rule of thumb developed from the average healthy disc (see section 3.2).[8] The ISNT Rule applies when the disc is round or vertically ovoid, but it has no merit if the scleral canal is asymmetrically shaped, tilted or horizontally ovoid. Determining the shape of the canal helps to understand whether the ISNT rule can be applied. In our GONE study, we found ophthalmology trainees have a much higher tendency to underestimate discs that are horizontally ovoid.[2] This is likely due to the uncommon disc shape making assessment of neuroretinal rim more difficult.

Accurate determination of the external margins of the disc is a critical step in the assessment of the ONH. Errors in the external margin include size, shape and tilt and are significantly contributed to by the extent and type of the PPA.

d. Background information

Although the normal disc is vertically ovoid with the vertical diameter around 10% larger than the horizontal one, there is a great deal of variation in shape. While it is true that there is less variation than in disc size, disc shape is a factor that requires conscious examination.

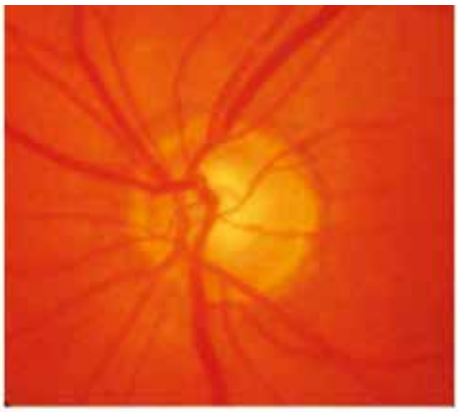
Ovoid discs are often associated with disc tilt (see 4.1). Tilt induces other changes to the ONH which can confuse the examiner. Tilt and shape are not exclusively linked – markedly ovoid discs may not be tilted, although most significantly tilted discs are more ovoid than normal.

Ovoid discs are associated with astigmatism – with the long axis of the disc orientated to the corneal astigmatism. Markedly horizontally ovoid discs are often ‘vertically’ tilted (see 4.1) – in this situation there is often a vertical hemi-field sensitivity difference on field testing. When accompanied by an unusual disc, the visual field results often create concern as to the whether the nerve is affected by glaucoma.

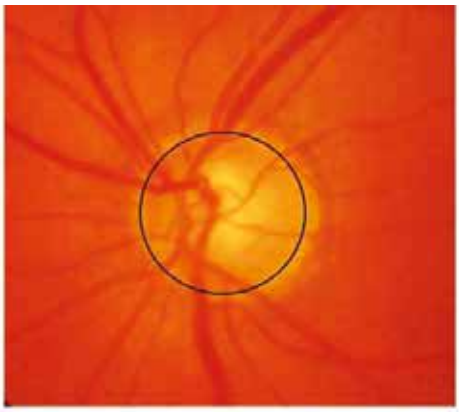
Remember that unusual nerves can have some accompanying field changes, but such observations may not explain all of the changes and there may be glaucoma as well as an underlying structural variation.

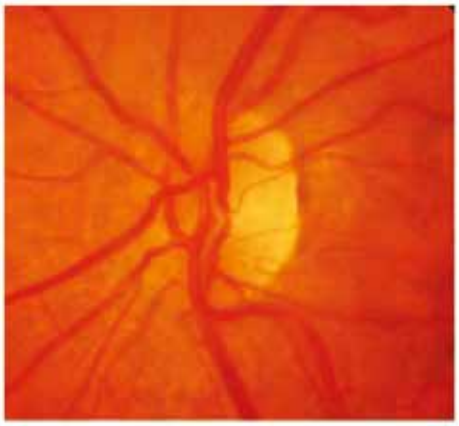
Stress and strain engineering modeling of the scleral canal suggests that the forces on the canal will tend to regularize the shape (approaching circular) and hypertrophy the scleral margin (‘ring’).

e. Examples

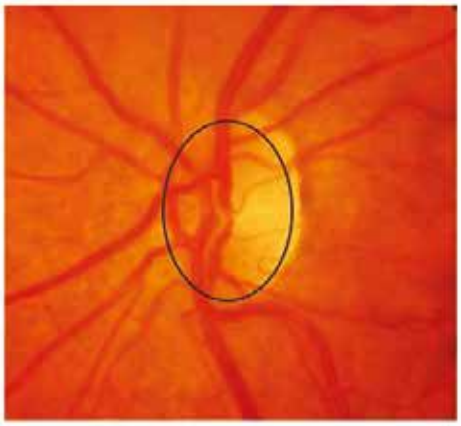


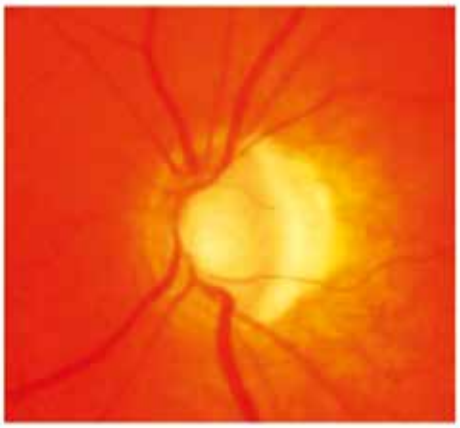
Medium disc, no tilt, round.



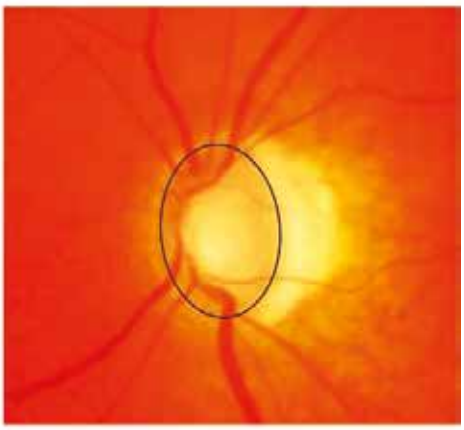


Small to medium disc, no tilt, markedly vertically ovoid.

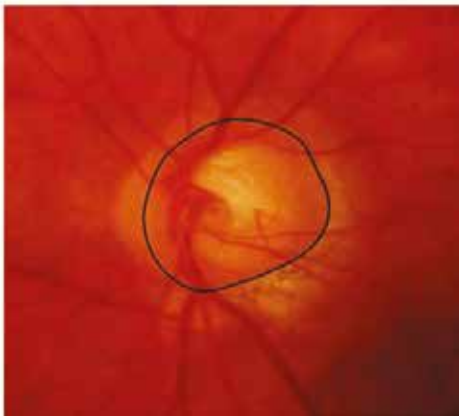


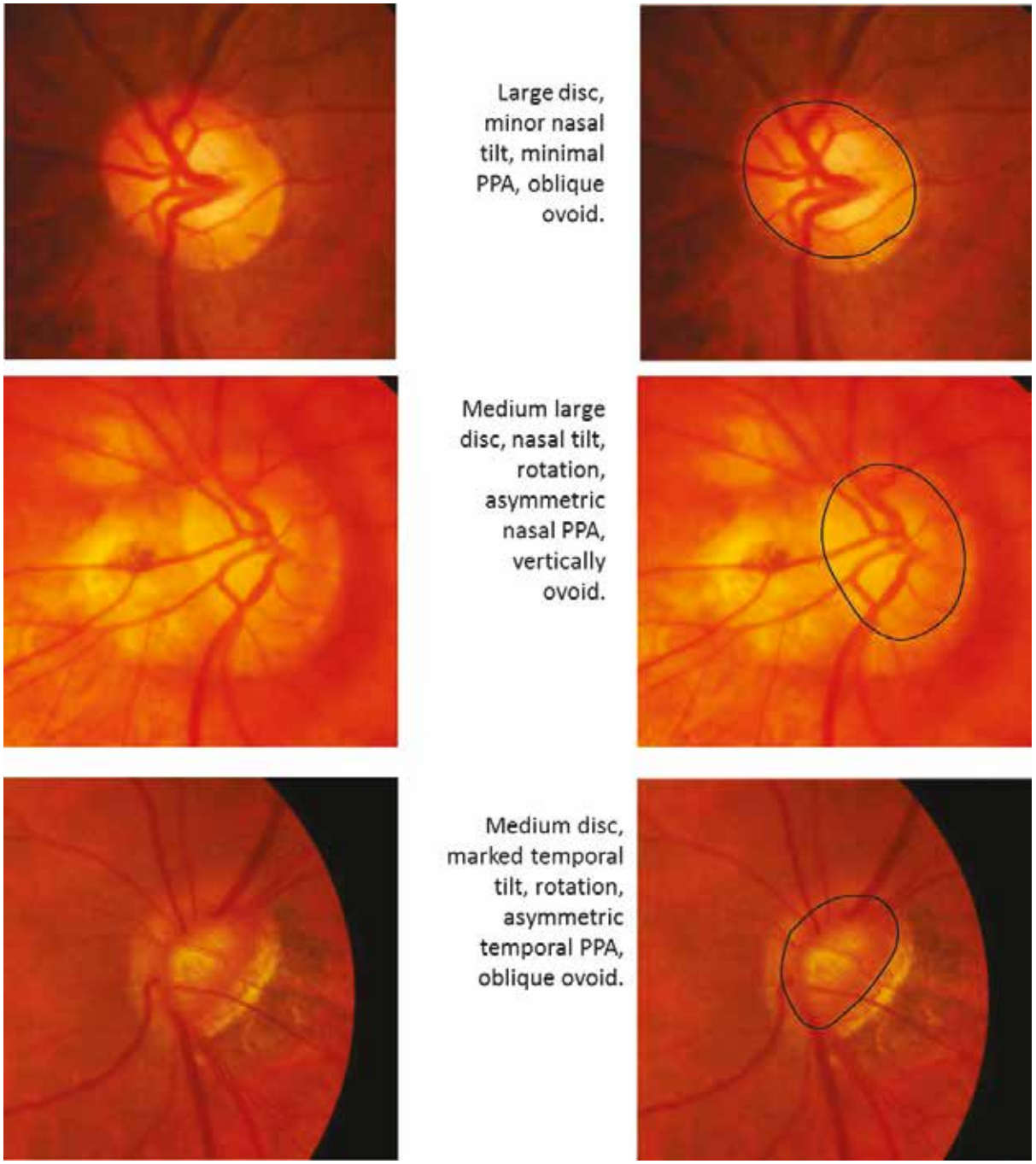


Medium disc, temporal tilt, asymmetric temporal PPA, vertically ovoid.

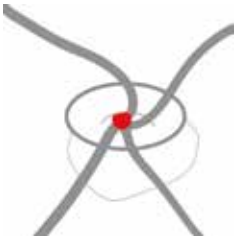


Large disc, minor temporal tilt with some rotation, asymmetric infero-temporal PPA, horizontally ovoid.





4.1 Disc Tilt



a. What is disc tilt?

'Disc tilt' is a term coined to identify a three dimensional aspect of the ONH. When considering the scleral canal we usually consider it exiting the eye directly backward from the eye – measuring the angle that the exiting nerve would subtend with the back of the eye would normally give a figure close to 90 degrees horizontally and vertically. More simply put: the nerve takes a direct course from the back of the eye to apex of the orbit after which it joins its fellow at the optic chiasm.

Thus, an ONH appears tilted when the exit direction is not aimed at the Optic Canal (at the apex of the orbit). If the nerve appears to head upward from the back of the eye then the 'face' of the nerve will seem to be directed inferiorly (vertical/inferior tilting). If the optic nerve appears to head toward the nose (horizontally) then the 'face' of the nerve is directed toward the temple (horizontal/temporal tilting). And if the nerve appears to be heading toward the temple, a line drawn out of it will aim toward to the nose (face aimed to the nose = horizontal/nasal tilting).

Vertical/superior tilting is very rare (nerve appears to exit downward and hence the ONH 'faces' upward).

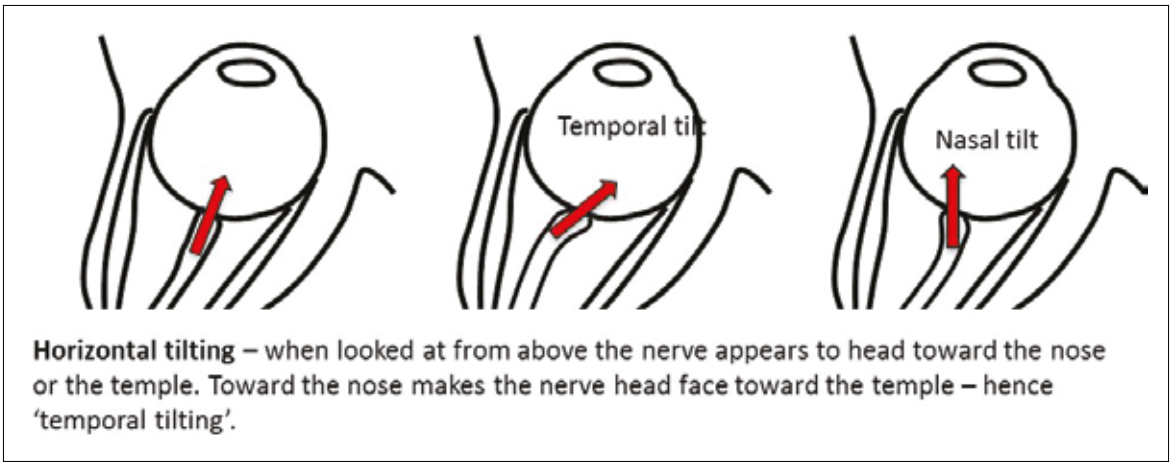


Figure 4.1.1: Horizontal, Temporal and Nasal tilting of the disc

Tilted discs are most often ovoid as well (see Shape 4.2). These discs may have corresponding hemi-field visual field defects. Vertical tilting of the disc can create a vertical hemifield disparity discovered on visual field testing (the upper half is different from the lower half) which can mimic glaucoma. Horizontal tilting can create horizontal hemifield disparity of the visual field which in turn may generate a suspicion of neurologic pathology.

The plane of the scleral canal may be flat or actually tilted, with one edge in front of the other. Such an arrangement will make accurate imaging with CSLO or OCT more difficult, and will be likely render the disc not comparable to normal databases. With care accurate scanning may be possible, and although the results may not be 'normal', these scans will provide valuable longitudinal data with which to follow the ONH. The clinical challenge in these nerves is to detect change over time – the hallmark of disease.

Tilted discs often have asymmetric PPA (see 4.4) and/or may have a marked scleral crescent. Scleral crescent and tilted ovoid discs are more frequent in myopia greater than -10 D. Detecting the margin of a tilted disc is more difficult and requires practice. Tilted discs are associated with astigmatism and the axis of the tilt relate to the axis of the corneal astigmatism.

b. How is it measured?

The position of the entry of vascular bundle (through the lamina) in relation to the disc margin is the best measure of tilt. In a disc without tilt, the vessel will be visible and central (in relation to the margins of the disc) as they pass through the lamina.

In a tilted disc, the vascular bundle enters eccentrically – close to one edge than the other. In cases of marked tilting, the site of entry of the vascular bundle may be obscured under the neuro-retinal rim.

The direction of tilt is named for the direction that a line would take if it were directed out of the nerve toward the examiner. So if the vascular bundle were on the nasal side of the disc (the disc may well be ovoid vertically, the nasal NRR heaped up), a line drawn out of the nerve toward the examiner will appear to be directed toward towards the temple (the nerve if followed behind the eye appears to aim nasally). So the nerve head 'faces' temporally and the disc is said to be tilted temporally.

The same construct applies to nasal and inferior tilting (see Figure 4.1.1).

There are no objective standards for the amount of tilting. We use direction (inferior, temporal, nasal) and amount (mild, moderate, marked). 'Mild tilting' describes an ONH where the position of the vessels is eccentric in the disc, but the disc may be normally shaped and there is no effect on the rim and plane of the nerve is flat.

Moderate tilting describes an ONH where the disc shape will be ovoid, there is an effect on appearance of the rim (asymmetry with one side appearing flat and the other 'heaped up') possibly with some asymmetric PPA.

Marked tilting describes buried vascular bundle root, markedly ovoid disc, usually with a scleral crescent and asymmetric PPA, and often with associated hemifield disparity on VF testing and corneal astigmatism.

c. Why is it important?

Markedly tilted discs have an ovoid shape, eccentric PPA with or without scleral crescent (enlarged blindspot), and significant asymmetry in the rim appearance. In addition, they can have visual field defects. They can pose significant diagnostic challenges.

In a tilted disc anterior margin (for example the nasal margin in a temporal tilt) tends to have a fairly heaped up neuroretinal rim, sometimes with a blurred disc margin, and often looks quite healthy (although sometimes scans on OCT a little thinning). This NRR will appear very different to the opposing edge that often looks quite flattened with an indistinct margin. This difference in NRR appearance can be quite compelling and needs to be consciously acknowledged as being a result of disc tilt.

Tilted discs can still be affected by glaucoma, and when they do, differentiating what is the normal state from what is pathological can be challenging.

In participants of the GONE program disc, tilt is a common cause of overcalling risk, particularly horizontal tilt.[2] Glaucoma most often causes a vertical disparity in disc appearance, so inferior tilting can cause incorrect level of concern as it can mimic this. The key to correct interpretation

of the ONH is systematic examination of, with understanding, the structure of the disc. Failure to detect tilt will mean that it is impossible to correctly identify a common cause of error in clinical examination.

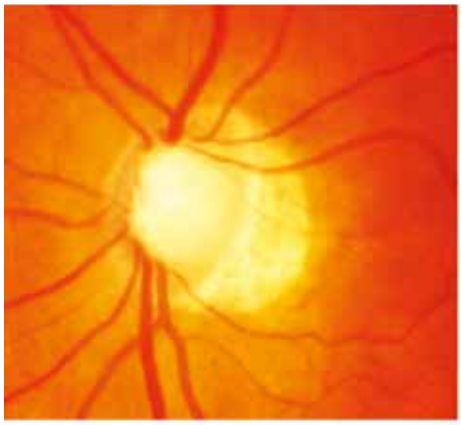
d. Background information

The position of the vessel trunk in relation to the margin has some association to the area of visual field defect. In addition, PPA has an association with NRR loss. Both are associated with tilt, which can be a normal variation.

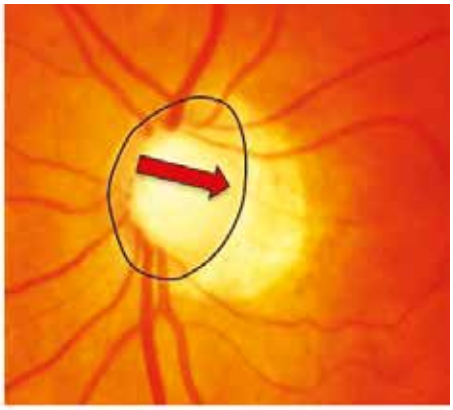
Disc tilt is most often associated with ovoid discs (see 4.2). Tilt induces other changes to the ONH which can confuse the examiner. Tilt and shape are not exclusively linked – markedly ovoid discs may not be tilted, although most significantly tilted discs are more ovoid than normal.

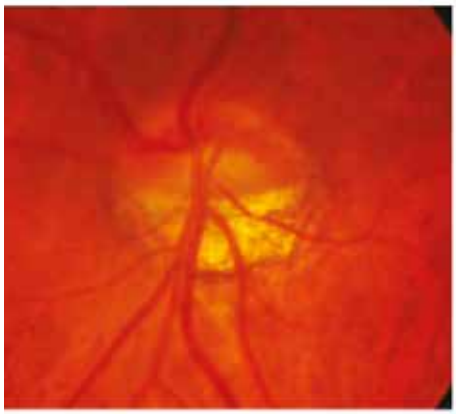
Ovoid discs and tilted discs are associated with astigmatism – with the long axis of the disc orientated to the corneal astigmatism. Markedly horizontally ovoid discs are often 'vertically' tilted (see 4.2) – in this situation there is often a vertical hemi-field sensitivity difference on field testing. When accompanied by an unusual disc, the visual field results often create concern as to the whether the nerve is affected by glaucoma.

e. Examples

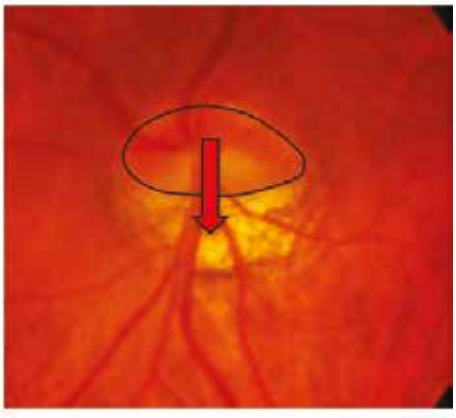


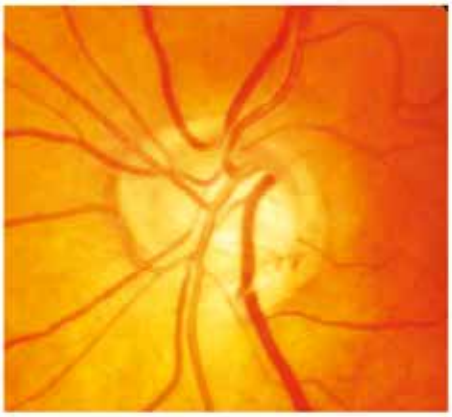
Temporal Tilting – vascular root is buried under the nasal rim, asymmetric temporal PPA. This is the most common form of disc tilt encountered.



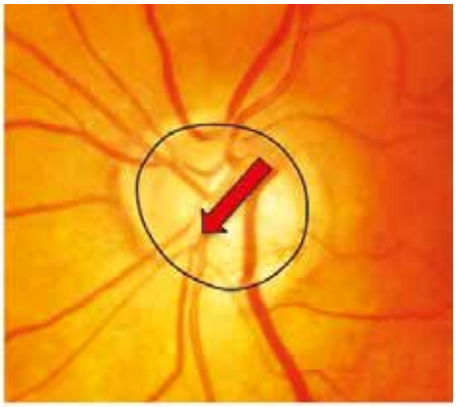


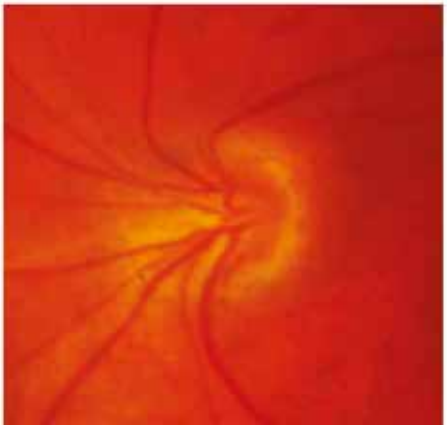
Vertical (inferior) Tilting – vascular root is buried under the superior rim, asymmetric inferior PPA. (Superior tilt is very rare).



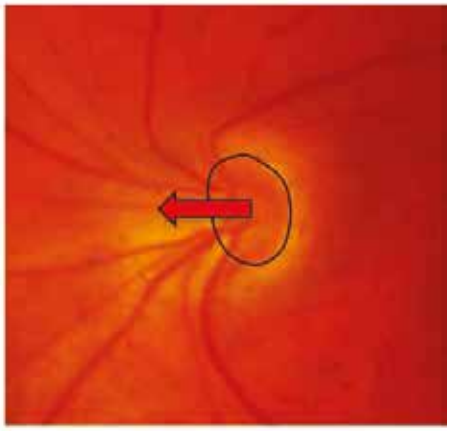


Oblique (infero-nasal) Tilting – vascular root is buried under the supero-temporal rim, asymmetric inferior PPA. (Notch in inferior rim may be congenital).





Nasal Tilting – vascular root is buried under the temporal rim, asymmetric nasal PPA. (Disc is hypoplastic).



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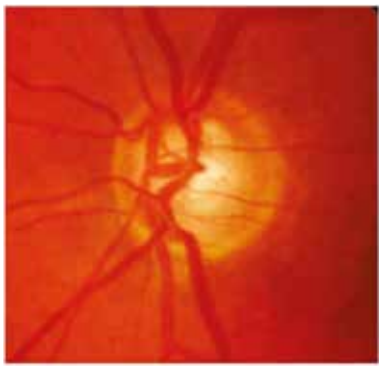
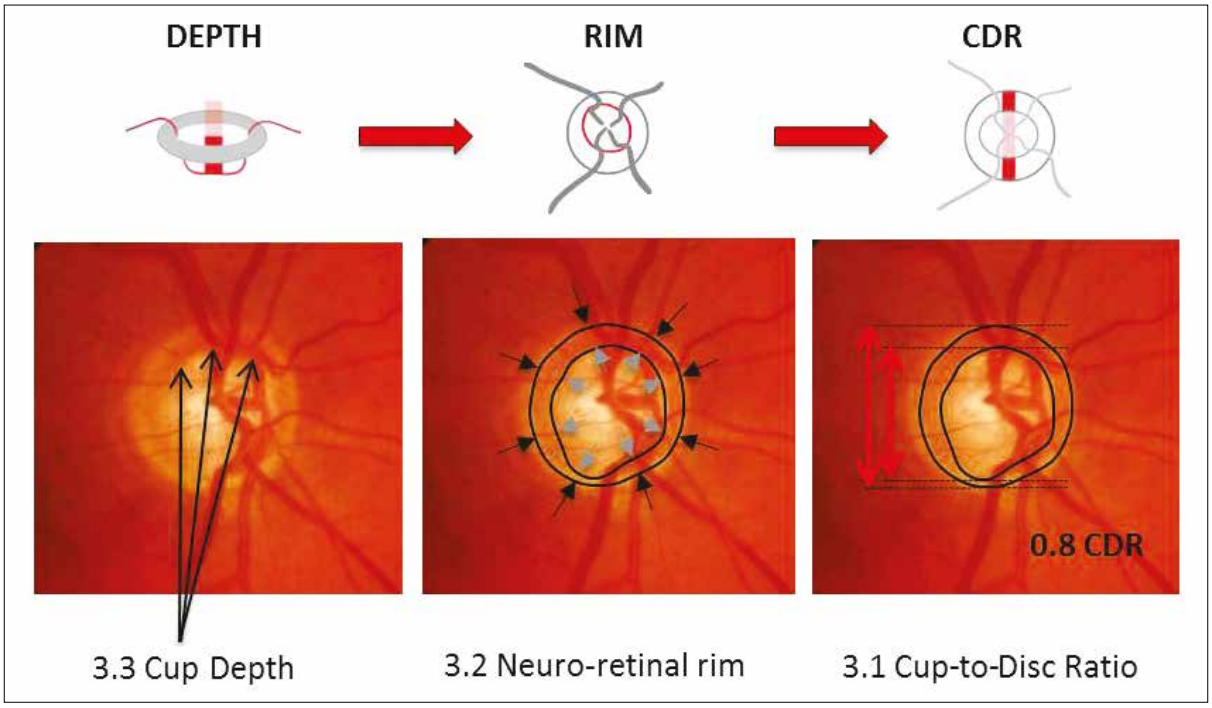
3 The "Inside"

This section is directed to the examination of the neural and glial elements of the disc. These are housed and supported by the structural elements (described in the previous section), and their appearance is significantly altered by them. We have included in this section the depth of the cup – which is mostly determined by the position of the lamina cribrosa, but sits most closely with the other assessments of the rim and thus is best fitted here. We start with the depth of the cup - we know from GONE that this influences our ability to discern the rim and influences our overall assessment of the pathology (deep cups tend to be thought of as more likely to be glaucomatous).[1] Next we look at the rim itself: identifying and determining the consistency of the rim, symmetry, conformation to the ISNT rule, and the presence of focal thinning (notches). Finally we will make an assessment of the CDR, which is disc size dependent but retains a high utility value in describing the extent of loss of disc rim.





3.3 Cup Depth

a. What is cup depth?

Cup depth is a physical feature that significantly affects the assessment of the ONH for glaucoma. It is not a feature that is (routinely) formally measured, although the depth is captured on most disc analysis machines.

On average, the depth of the cup increases with the size of the disc as the neuroretinal tissues spreads out over a greater scleral opening area. But there are large discs with shallow cups and relatively small discs with deep cups. It is unusual to see a very small disc with a deep cup.

The cup depth is determined by the position of the lamina cribrosa in relation to the scleral layer. It ranges from being almost in the same plane, such as in myopic colobomatous posterior segments, to deeply excavated discs. Such variation may be within normal limits, but the deepening may result from pathological posterior bowing of the lamina cribrosa.

The depth of the cup is also influenced by the loss of the meniscal tissue in the base of the cup. Loss of this tissue makes the lamina more visible. Baring of the anterior surface of the lamina contributes to some of the other features of glaucoma: (apparent) increase in the lamina pores, widening of the lamina interstices, nasalization of the vessels.

There is a significant degree of variation in cup depth in the absence of glaucoma. Cup depth has been shown to have a similar level of heritability as CDR (see 3.1), so members of a family may share similar disc appearance, including the depth of the cup. The physical changes to the ONH in glaucoma will vary depending on the starting appearance.

Elevated intraocular pressure has been shown to cause pathological bowing of the lamina and result in an increase the depth of the cup in animal models. This has also been observed in human eyes. In humans with glaucoma, on an average, those with the highest pressures have the deeper cups. Cup depth has been shown to vary over the short term with IOP, being shallower when the IOP is lowered in the same eye.[2]

Reversal of cupping in young patients (and some older patients) on lowering the IOP is due to anterior movement of the lamina and remodeling of glial elements in the nerve head. In these eyes the cup depth is noted to be shallow.

Exceptions to these observations are common, particularly with smaller discs and glaucoma, acute angle closure glaucoma, and in inherited patterns of disc change. It is possible to have glaucomatous visual loss without deepening of the cup, a situation where NRR loss is more difficult to detect. Small discs show less pronounced features of ‘cupping’ making it more likely to under-appreciate their risk of glaucomatous change.

In the GONE study, a deeper cup is a feature linked to the recognition of glaucomatous change in the ONH. Where the cup is shallow, there is less likely to be recognition of glaucomatous change.[1]

b. How is it measured?

Cup depth is formally measured from the level of the Bruch's (when present) to the anterior surface of the lamina cribrosa. The cup depth is measured (with varying degrees of accuracy) by machines, such as the OCT and HRT. Reflectance measurements will not measure the position of these structures, rather they infer them by the surface contour.

In practice, there is no merit to the measurement of cup depth as cup depth itself tells little about the health of the neuroretinal tissues. When we asked glaucoma subspecialists to perform disc examination with monoscopic viewing and stereoscopic viewing, while cup depth is more consistently assessed in stereoscopic condition it did not have any significant bearing in the overall assessment of neuroretinal rim or glaucoma risk.[3] Nonetheless, it is a feature that warrants formal observation and categorization because incorrect assessment of cup depth by ophthalmology trainees alter their interpretation of the optic disc.[1] We use shallow, medium and deep to describe this feature. Examples follow.

From the GONE study we can observe that cup depth influences how we assess the rest of the disc, but this makes sense as well. Deeper discs cups to be easier to assess the NRR, with the corollary that shallow cups (such as the myopic disc) can be challenging to assess the rim volume. The GONE project has shown that ONH with shallow cups are less likely to be assessed correctly, and are more likely to have their risk of glaucoma underestimated.[1]

c. Why is it important?

Cup depth is an important clinical feature to identify. We know from data from the GONE study that it independently influences the assessment of the risk of glaucoma.

Deeper cups invite a diagnosis of glaucoma: deepening of the cup can be a sign of elevated pressure, and often the more marked 'cupping' cues us to consider the diagnosis where it might not otherwise have been. Deep cups, by their nature, are often easier to assess, and occur more often in larger discs with larger CDR, thus (again) inviting consideration of glaucoma. On the other hand, the marked contour changes that come with a deep cup allow easier and more accurate NRR/CDR assessment.

Conversely, ONH with shallow cups are more difficult to assess: there are less clues as to the NRR margin (the 'inside') and often we need to use subtle vessel curvature signs to reliably identify the inner margin of the NRR. This is particularly apparent in 'saucerised' (after cup and saucer) discs (shallow cups) where there are focal notches in the NRR.

Myopic NRR loss (often larger, flatter and ovoid discs) is easy to miss: these discs can be difficult to assess and there have been a number 'missed' with very poor outcomes probably because of the myopic configuration.[4]

d. Background information

Studies performed recently with long term experimental models of glaucoma in monkeys (similar ONH structure to humans), pioneered by Claude Burgoyne, have elucidated the structural changes that result from elevated intraocular pressure.[5] These animals have had laser to markedly elevate their IOP. He (and others) have found that elevated IOP produces a posterior bowing of the lamina, with thinning and compaction.

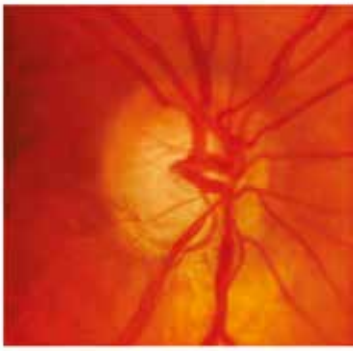
Interestingly, Burgoyne also found that the lamina movement occurs because the posterior layers of the sclera (from which the lamina is derived) tear away from the anterior layers. This is a little like plywood splitting, and the effect is to allow the lamina to recede significant back from its origin, and probably to place the vascular supply to the ONH in jeopardy.[5]

Evidence from the GONE study and elsewhere suggests that deep cups tend to get 'overcalled'. Using reflectance machines to assess contour can get variable results with deep cups because of the parallax issues (changing the position of the receiver by a few degrees can alter the appearance of the cup).

e. Examples

Shallow cup with cup margins that are unclear. Often called saucerised or sloping rims. It is often difficult to give a precise CDR.

Moderate cup depth. Rim delineation is possible and lamina features are visible. There is clear change in direction of retinal vessels as they cross the margin. A wide notch (such as this one) may not be as obvious as with a deep cup.



Deep cup. Rim delineation is usually straightforward. There is temporal tilting in this disc so the temporal margin is less distinct than the nasal. Some vessels are lost as they course forward to the retina from the lamina.

3.2 Cup Shape

a. What is cup shape?

Cup shape is term used to describe the 'inside' – or the inner margin of the neural tissues. Cup Shape is another way of describing the evenness or regularity of the Neuro-retinal rim (NRR). The neuro-retinal rim is defined by the disc margin on the 'outside' and the cup margin on the 'inside'. It is sensible and useful to describe the NRR itself, however such an approach does not allow easy redressal of errors in assessment. We have chosen to focus on the margins of the NRR for attention and feedback as we have noted that errors in NRR assessment have either occurred from mistaking the 'outside' boundary, or the 'inside' margin, or possible both.

Assessing the health of the NRR is the key objective of ONH examination for glaucoma (and other diseases). A symmetric cup suggests a normal nerve or symmetric loss of NRR ('concentric cupping'). The presence of irregularity, or identifiable focal loss of NRR (a 'notch'), is strong evidence of pathology (although examples of non-progressive 'pits' exist).

Glaucoma is most often an asymmetric disease: it may be asymmetric across the horizontal midline in one eye (difference between the upper and lower) and/or between the eyes. Asymmetry in the NRR is thus a key finding. Glaucomatous defects may be relatively focal or diffuse with concentric loss of neuroretinal rim.[6]

Concentric loss of the NRR produces an even reduction in the rim and (usually) relatively easy to determine cup dimensions. Focal loss of the NRR, particularly if it is around vascular bundles, can be difficult to detect. Non-concentric loss of the rim produces an uneven shape to the cup – initially this is an eccentric cup (with a thinner rim in one area) which develops into a notch, and then finally a 'full thickness' notch where there is no residual rim in that area.[6]

b. How is it measured?

Cup shape (or delineation of the internal margin of the NRR) is measured at examination or by machine. In clinical examination the inner margin is detected by a change in contour or color, or both.

Demarcation of the contour change requires practice. Color changes may be obvious (clear disc margins, deeper cups) but can also be harder to differentiate and hence be less informative. Often subtle contour changes in the neuroretinal rim can be highlighted by a change in the curvature of blood vessels crossing the inner margin of the cup. Therefore, careful and close look at the course of blood vessels at the optic disc is often fruitful and is a skill that needs to be practiced. In many instances, contour changes are easily detected – but irregular rim loss and shallow cups make the process less reliable. Recognizing discs that are inherently more difficult to accurately assess is an important step in improving ONH assessment.

Certain patterns of cup change (or NRR change) are typical of glaucoma loss. The ISNT rule describes the normal arrangement of the NRR in descending order of thickness. Most often the

Inferior NRR is the thickest, followed by the Superior, then Nasal, then Temporal. (Note that the upper field is more sensitive with more axons supplying it, but the fovea is inferior to the disc so more axons exit via the inferior pole than the superior).[7]

If the NRR does not obey the ISNT rule then it is not normal. It may not be normal because the structure of the disc is also not normal – tilted, ovoid, or odd in shape. Or it may be that the disc structure is normal and loss of the NRR has produced a loss of the normal ISNT relationship. In theory, concentric cupping may cause even loss of NRR and preserve the ISNT arrangement but glaucoma loss is most often asymmetric with more focal loss (hence the reason for the typical visual field defects).[7]

The areas in which most people fail to detect focal thinning are at the superior and inferior poles and on the nasal side. Nasal thinning can often be obscured by the vascular trunk, which may not marginalize and thus obscure what can be really quite a thin rim.

The most common field defect we see in glaucoma is a superior and inferior arcuate scotoma, which is usually within 20° of fixation. That puts focal loss of neuroretinal rim between superior and inferior pole and two clock hours temporal as the most likely place. Sometimes, focal peripapillary atrophy will help identify it as well as retinal nerve fibre layer loss.

In our study of glaucoma sub-specialists, we found there is no difference between monoscopic and stereoscopic viewing in the assessment of cup shape. This is likely because glaucoma sub-specialists are more accustomed to use other cues such as subtle blood vessel curvature change to determine the inner margin.[2] For trainees, we suggest stereoscopic viewing through dilated pupil will help better identify focal NRR defects. Particular care needs to be taken where there is some other anomaly of the disc, such as horizontal tilting, where focal notches can be difficult to pick up in the superior and inferior poles.

c. Why is it important?

Many years ago, a system of description of disc pathology in glaucoma was developed, which included such terms as focal ischaemic and concentric cupping. Although there is probably no underlying pathological legitimacy to these groupings, there is some clinical merit in understanding that the 'typical' appearance of glaucoma damage is just that – it is not universal. Witness the typical changes with acute pressure rise (AACG, Trauma, Retinal surgery, etc) there is often little cupping, instead there is more of a flattening of the nerve and loss of RNFL on OCT and functional decline. Elevated IOP is also not the only cause of typical cupping, and cupping may originate from other causes ('physiologic', some toxic optic neuropathies, ADOA, and some others).

Some discs under glaucomatous stress become the typical deepened, excavated cup with thinning and sometimes undermining of the neuroretinal rim with bayonetting of vessels, nasalisation of vasculature, opening of the lamina interstices and sometimes some PPA changes. But glaucoma can also occur almost with isolated notches without a lot of diffuse excavation, and nerve fibre

layer loss and the resulting functional loss can occur with only subtle changes in neuroretinal rim architecture.

We found that focal defects in neuroretinal rim or notches were commonly missed in the GONE program by trainees.[8] Missing these findings represented a significant risk for underestimating the risk of glaucoma.[1]

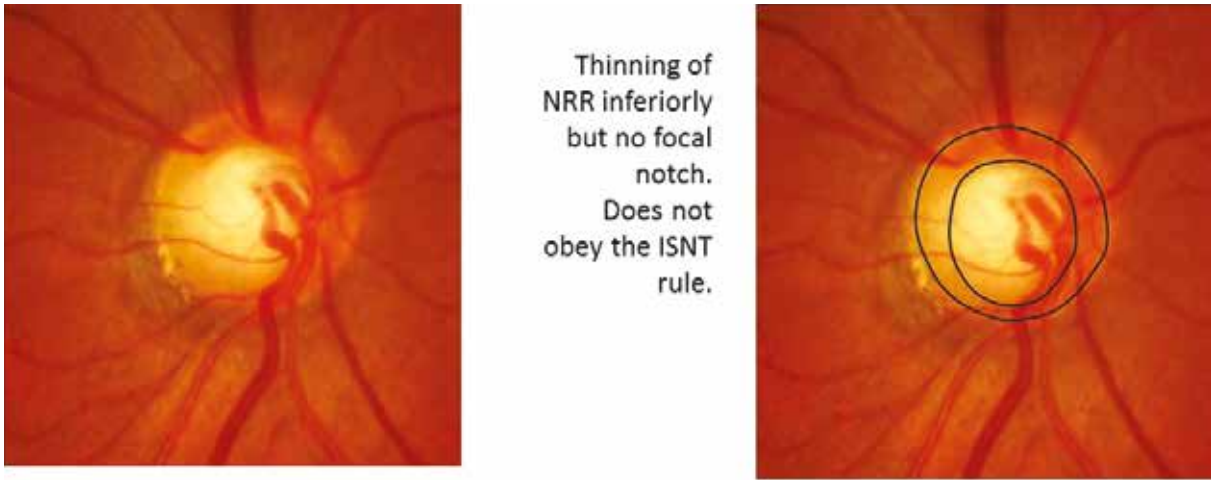
d. Background information

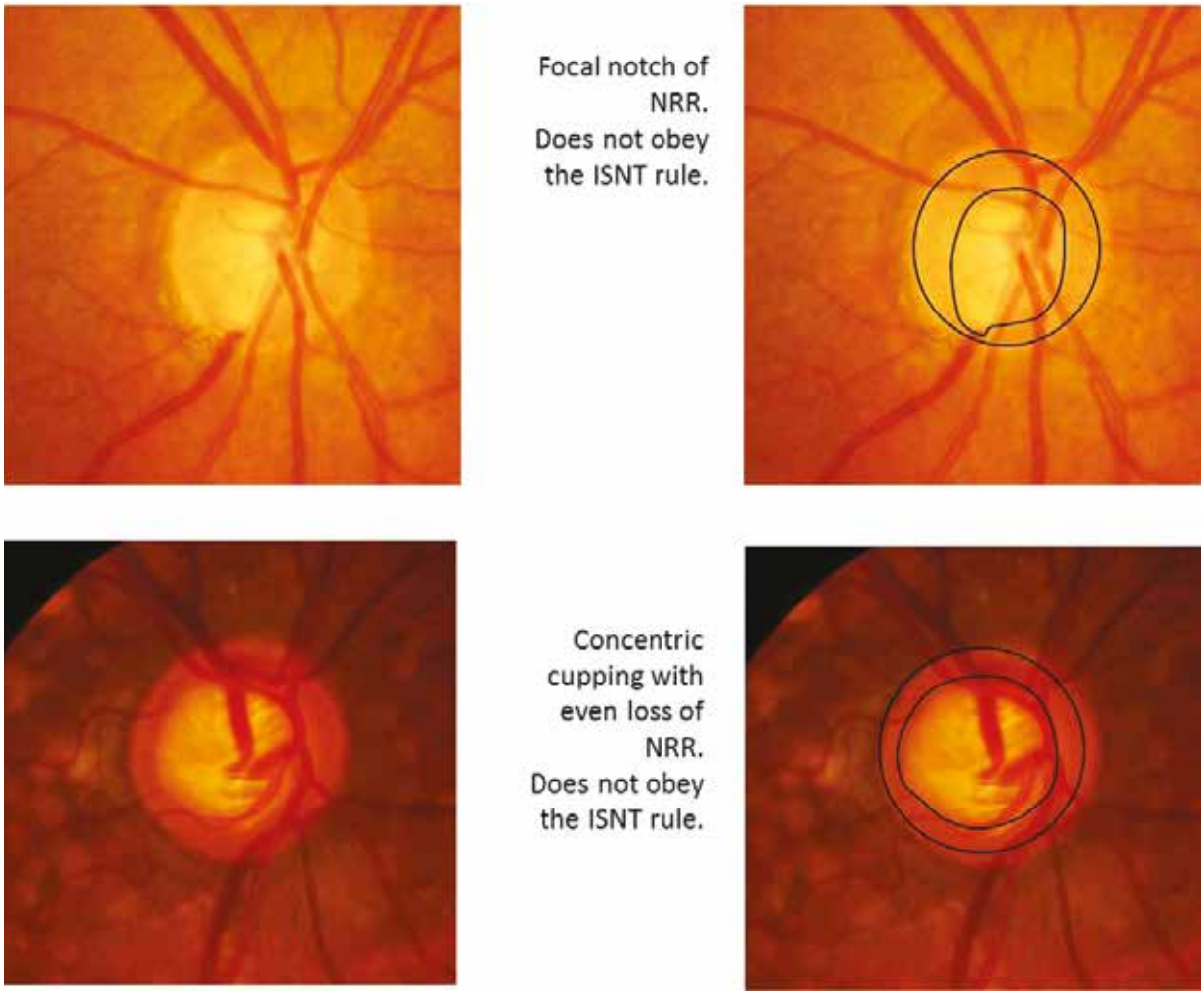
The determination of the cup shape, along with CDR and delineation of the external margin of the disc, are the pieces of information used to calculate NRR size. NRR size is highly variable – varying mostly with the disc size (the larger the disc the larger surface area of the NRR). The NRR follows a typical shape in a 'normal' disc – the ISNT rule describes the arrangement of the NRR width from largest to smallest (Inferior, Superior, Nasal, Temporal).[7]

Loss of NRR often precedes functional change, but the pattern of visual field change is related to the anatomic loss. The most commonly recognized form of functional glaucomatous loss is the arcuate scotoma which corresponds to superior and inferior pole focal changes. The axons in the ONH are arranged retinotopically and the corresponding anatomic location for scotomas within 20° of fixation is close to the superior and inferior pole of the nerve. (This arrangement is less clear where the disc is rotated or tilted).

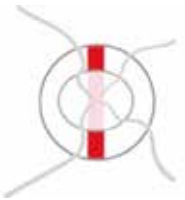
Overall reduction in sensitivity is also a well recognized feature of glaucomatous visual field change, which is associated with diffuse neuro-retinal rim loss. Nasal step is usually due to defects at the 6 or 12 o'clock position, and hemifield disparity relates to greater loss of neuro-retinal rim in one half or the other. Other variations in visual field loss exist, including paracentral defects (more commonly seen in 'low tension' glaucoma) and macular loss, which can rarely be part of the glaucomatous spectrum.

e. Examples





3.1 Cup-to-Disc Ratio (CDR)



a. What is CDR?

The Cup-to-Disc ratio (CDR) is an indirect measure of neuro-retinal rim (NRR) area. It is defined as the ratio of the vertical dimensions of the optic cup over the vertical dimension of the disc. As it is a ratio it is independent of magnification, but the normal range varies with the disc size. Larger discs have larger normal CDR, and smaller discs are likely to be pathological at lesser CDR than the larger disc.[9]

The CDR is the oldest but still the most widely used descriptor of optic nerve health. It has (reasonably) come under fire in recent years for being misleading. Critics have argued that CDR is so dependent on disc size as to be meaningless. Certainly in the day and age of measurement of the disc, NRR, RNFL and the ganglion cell layer the measurement of CDR seems passé.

But the measure of CDR retains utility: as a single number, it is a indicator of severity in most glaucoma practices/clinics and correct evaluation of the CDR is the single most important discriminating factor associated with successful disc assessment for glaucoma (based on the GONE data).[1]

b. How is it measured?

Simply, the CDR requires the accurate assessment of the external margin of the disc (or the scleral canal size – the 'outside'), coupled with the correct demarcation of the cup margins (the 'inside').

Cup-disc ratio is measured vertically. Correct identification of the disc margins is covered in other chapters. In short, it requires understanding of the underlying anatomy of the disc (size, shape, tilt and the effect of PPA) the parts of which are covered in 4.4, 4.3, 4.2, and 4.1. In order to accurately identify the cup margins, an understanding of the depth and regularity (shape) of the cup, which are covered in 3.3 and 3.2 is required.

CDR can/is measured by machine (CSLO or OCT). When using data derived from machine, it is valuable to correlate it with examination findings. Machine algorithms require certain assumptions to be made about where the cup should be measured and where the disc rim lies. In general, those discs that pose more challenges for the examiner in assessment will also produce variable quality machine based results.

c. Why is it important?

The measure of CDR remains in wide clinical use and still describes (albeit imperfectly) a feature of importance in the examination of the ONH. For example, a CDR of 0.9 is very rarely normal (unless in a very large disc). But the limitation of the CDR is that it is contextual with the disc size and does not capture the presence of focal changes to the NRR. For instance, an eye with 0.6 CDR can be normal in a large disc but can be abnormal for a small disc or if there is marked asymmetric loss in either superior or inferior poles of neuroretinal rim.

CDR is important in assessing disc examination ability as its correct assessment is a compound skill requiring the ability to correctly discern the disc margin as well as the cup margin. As a single measure, it more accurately represents the examiner's ability to correctly identify structures in the ONH than any other feature.

Incorrect assessment of the CDR can occur from errors in judging the 'outside' (the disc margin) or from errors on the 'inside' (the cup margin). Thus improving the CDR 'score' usually involves revisiting the disc margin or cup margin skills (see previous chapters).

d. Background information

The normal CDR can range between 0.0 to 0.9 in ONHs, but 98% of nerves will have a CDR of 0.7 or less.[10]

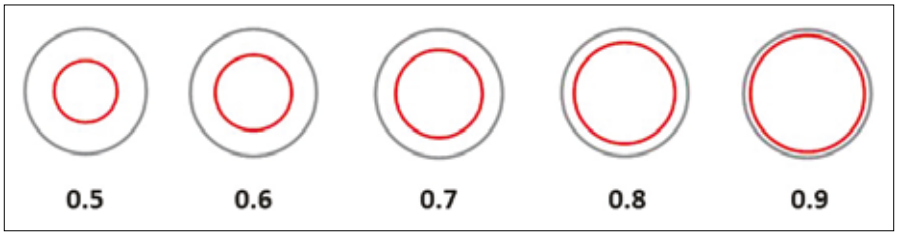
Less than 10% of normal eyes have 0.1 or greater CDR difference between the two eyes. A difference of 0.2 CDR between each eye requires an explanation (such as disc size asymmetry or possible disease).[11]

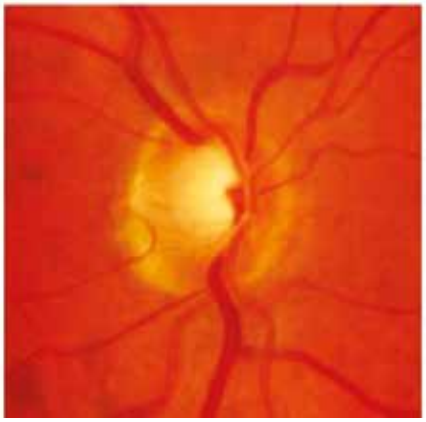
Less than 10% of normal discs have a cup that is horizontally larger than vertical. Glaucoma tends to cause the vertical dimension of the cup to increase quicker than the horizontal (the superior and inferior NRR thins).

Cup-disc ratio is, in normal populations, inherited. This should not surprise as disc size is inherited as well, and the chief determinant of CDR is disc size.

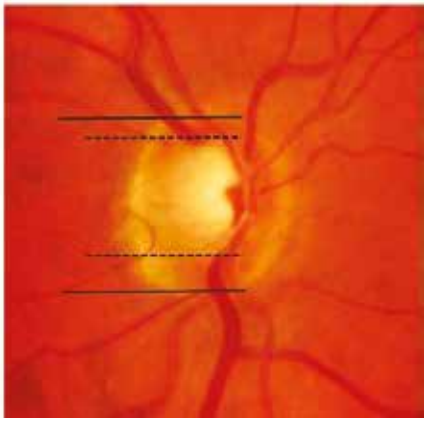
Accuracy in CDR measurement becomes quite poor under 0.5 CDR but the clinical importance approaches zero and thus we will not focus on it in this teaching system.

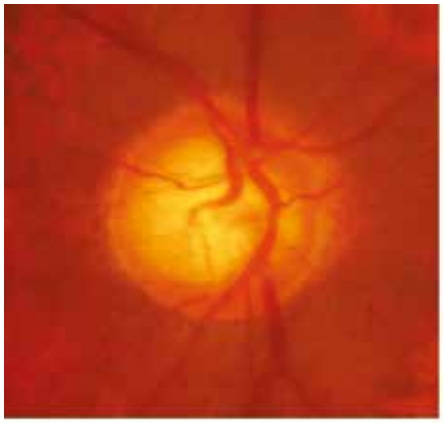
e. Examples



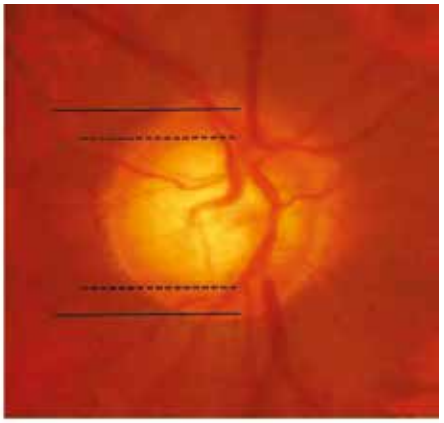


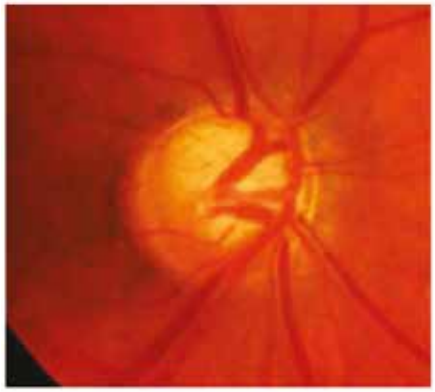
CDR – 0.7
Small - medium-sized disc minor temporal tilt.



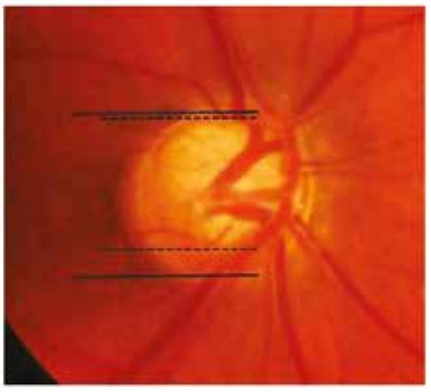


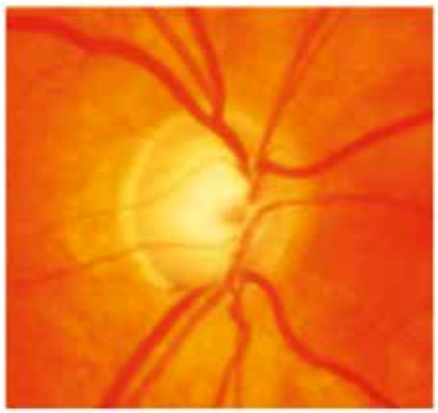
CDR – 0.7
Large-sized disc with no tilt. Thinner rim nasally and temporally.



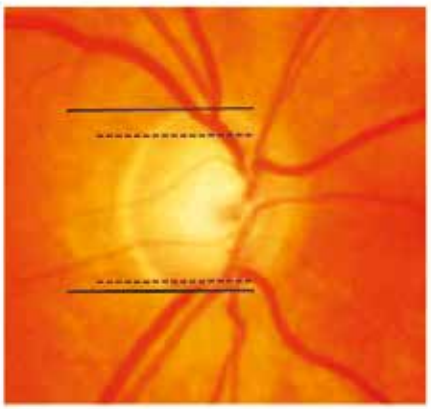


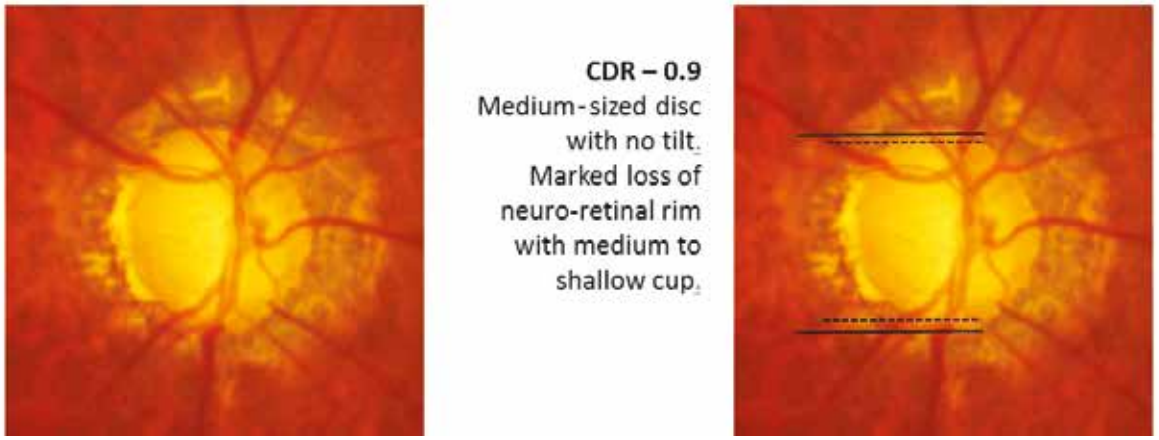
CDR – 0.8
Medium-sized disc with no tilt. Marked loss of superior and nasal rim.





CDR – 0.8
Medium-sized disc with minor temporal tilt. Marked loss of inferior rim with disc hemorrhage.





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4 Confirmation

This section is directed to the examination of two key glaucomatous features: focal or diffuse thinning of the Retinal Nerve Fibre Layer (RNFL), and Disc Rim Haemorrhages (so-called "Drance" Hemorrhages).[1] These are grouped together as they may often occur in proximity, and both can be difficult to pick up, but they can contribute significantly to glaucoma risk assessment.[2,3] RNFL loss is one of the more difficult physical signs to elucidate, particularly diffuse loss. The advent of the high resolution OCT of the RNFL can quantify and monitor this which clinical examination alone cannot.[4] Drance Hemorrhages occur across the disc margin and can last several weeks to months. Their presence is neither diagnostic of glaucoma or progression, but several studies have shown their association with glaucoma and with worsening of the disease.

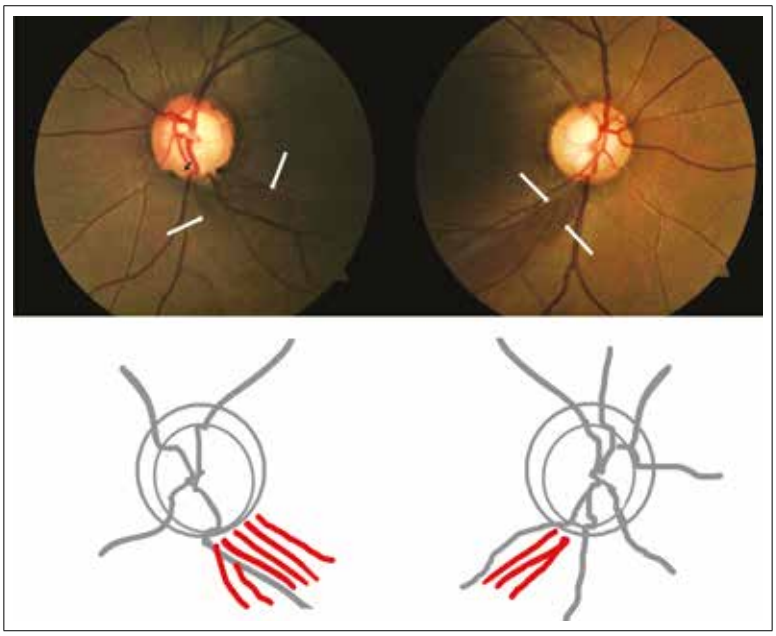


Figure 4.1: Retinal nerve fiber layer defects in glaucoma (white arrows)
(Photo courtesy: Dr. Talvir Sidhu)

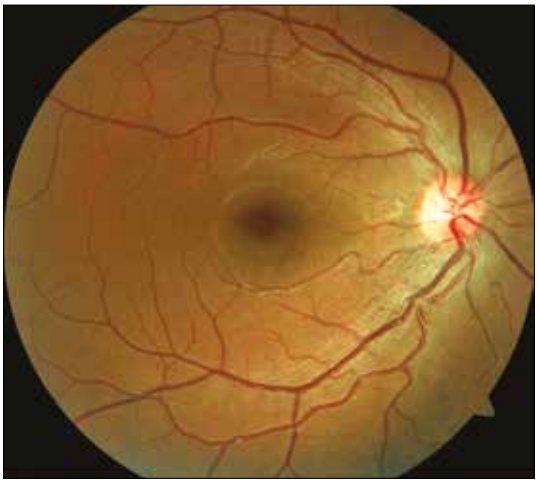


Figure 4.2: A normal retinal nerve fiber layer distribution. (Photo courtesy: Dr. Talvir Sidhu)

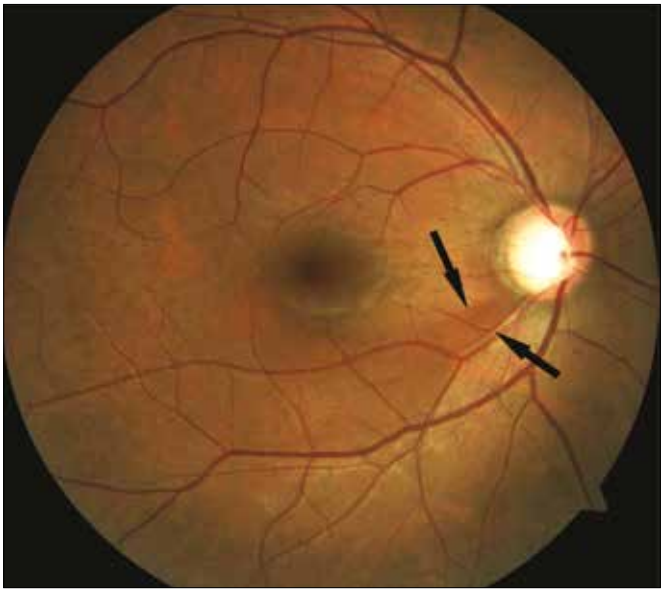


Figure 4.2: Retinal nerve fiber layer defect (marked by black arrows)
(Photo courtesy: Dr. Talvir Sidhu)

2.2 Retinal Nerve Fibre Layer (RNFL) Defects

a. What are RNFL defects?

'RNFL defects' are clinically evident areas of RNFL thinning: they are wedge shaped defects that aim toward the disc margin. (Figure 4.1, 4.2) They are assumed to always be pathological although they can result from other pathology (eg vascular, drusen). They need to be differentiated from small slit-like defects (usually more than one disc diameter away from the disc margin) which are normal findings.[5] (Figure 4.3)

RNFL defects are classified as focal or diffuse. Focal defects correspond to 'notches' in the NRR and to focal visual field defects (mostly arcuate scotomas) see chapter 3.2. Diffuse loss of the RNFL is manifested by relatively even reduction in the thickness of the RNFL and may correspond to concentric cupping (with even rim loss) and overall reduction in sensitivity on visual field testing.[5,6] (Figure 4.4)

In reality, there exists a scale from focal to diffuse. Some defects are restricted to one half of the nerve and produce wide defects in the NRR.

In general, detecting RNFL defects takes some practice- this is an area where photographs or dilated indirect ophthalmoscopy can be more helpful than direct ophthalmoscopy. It is possible to take and process photographs of the RNFL to increase the visibility of the RNFL defects (by desaturation (removing the colour) and by heightening contrast). Although photographs managed for maximal RNFL identification improve the detection of defects, some disc photographs make the detection of the RNFL difficult.

RNFL defects are easier to detect in younger patients (because of a reflective ILM). Normal

RNFL either side of an area of deficit makes for easier detection. There is an age dependent loss of RNFL that makes detection more difficult in the aged.[7] Experimental studies suggest that around half of the axons need to be lost before the RNFL defect is clinically detectable.

Diffuse loss of retinal nerve fiber layer is often associated with baring of the retinal vasculature. (Figure 4.5) Mostly retinal vasculature will appear partially submerged in the inner layers of the retina, but when there is significant loss, the vessels become more visible and there is a less reflective or translucent appearance to the retina itself.

The advent of spectral domain OCT has made this clinical skill less valuable in following patients with glaucoma. It is still very valuable in screening and in early glaucoma diagnosis where functional tests are not helpful.

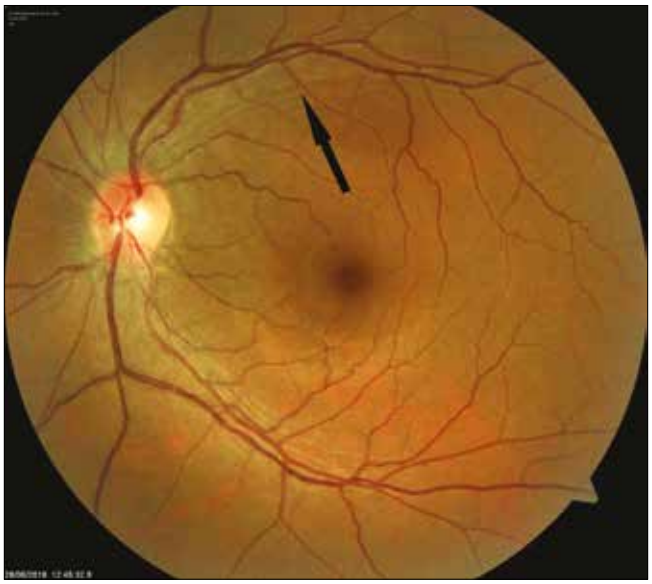


Figure 4.3: Slit-like RNFL defect away from disc margin in a normal eye.
(Photo courtesy: Dr. Talvir Sidhu)

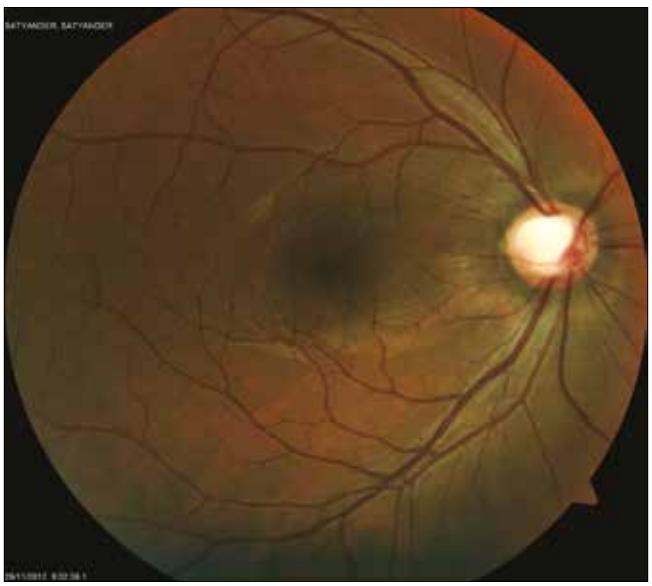


Figure 4.4: Concentric cupping with diffuse RNFL loss. (Photo courtesy: Dr. Talvir Sidhu)

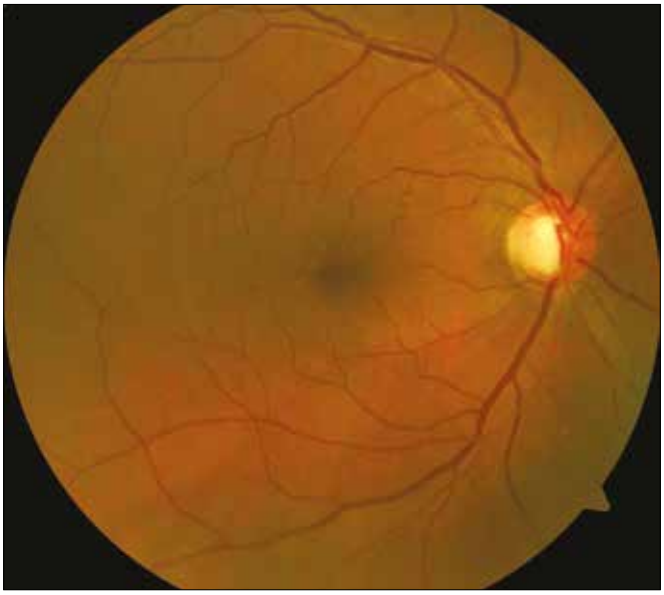


Figure 4.5: Inferior notch with wide RNFL defect leading to prominence of vessels in inferior arcade. (Photo courtesy: Dr. Talvir Sidhu)

b. How is it measured?

On clinical examination, RNFL defects are rarely measured: they are identified and their position and lateral dimension noted. The presence of an RNFL defect is strong evidence of a pathological process and thus the recognition of RNFL defects is a valuable addition to clinical features.

Measurement of RNFL defects is now performed reliably by spectral domain OCT. Although clinical examination can detect defects, they are not reliable methods of quantifying the defect. OCT of the RNFL creates a mass of data about the volume of the RNFL and is mostly reliable.[8] OCT machines need to discern the outer margin of the RNFL and relatively often make errors creating an artifact of change. Most machines will show the image of the RNFL with the machine drawn boundaries that allows the clinician to check. This is a clinical skill that also requires practice but is beyond the scope of this course.

RNFL defects on clinical examination can be drawn out using retinal vasculature as markings. Most often they will be associated with focal defects in neuroretinal rim, although sometimes these will be difficult to detect.

RNFL defects are measured within one disc diameter of the disc margin. Defects or apparent defects further out than this are not classic retinal nerve fiber layer defects.

c. Why is it important?

All the clinical features of glaucoma (including visual field testing) have variation, both in individuals compared to the population, and between tests in the same patient. Thus, unequivocal findings are very helpful in directing further testing and treatment. For example (see photos below), large discs have larger CDR and can look pathological, but may not be. The presence of an RNFL defect makes this disc unequivocally glaucomatous.

RNFL defects are always pathological as they represent relatively recent change. Focal loss in childhood will generally become less apparent with time as axons redistribute. RNFL defects can be found in other conditions, but they are not present normally.

Our study using GONE project showed that the failure to detect RNFL defects by ophthalmology trainees is the strongest predictor for underestimation of glaucoma risk. Underestimation of glaucoma risk is almost 10 times as likely if RNFL defect is missed by trainees.[1]

d. Background information

The normal RNFL is unevenly distributed: it is thickest at the superior and inferior regions (which correspond to the thickest NRR). The RNFL is most visible infero-temporally and supero-temporally. RNFL defects are easier to detect where it is thickest, giving the greatest differentiation of adjacent areas from normal to abnormal.

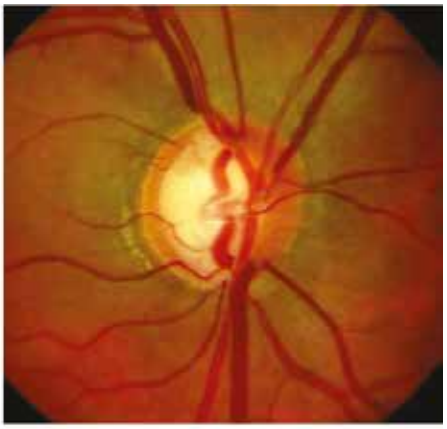
RNFL defects are rarely detected nasally, and infrequently in the temporal 4 clock hours. In these areas assessment of the rim is more valuable.[9]

RNFL defects are found in about 20% of glaucoma patients and are most likely to found earlier in the disease. More advanced glaucoma produces some diffuse loss which disguises focal changes. In general, we use structural evidence (ONH, RNFL) for following earlier disease.[10] and functional tests (VF testing) for following more advanced glaucoma.[11]

RNFL measurement (via OCT) has become the dominant method of investigating the health of the optic nerve. The quantification of the RNFL allows longitudinal change analysis and the RNFL is less normally variant than other ONH features.

e) Examples

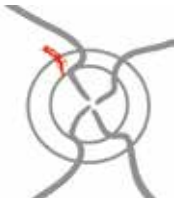
Retinal Nerve Fibre Layer (RNFL) defects are normally associated with notches or focal loss in the neuro-retinal rim, as they are here. There is a pronounced defect in the supero-temporal rim, and another more subtle loss inferiorly.



Retinal Nerve Fibre Layer (RNFL) defects can be hard to identify. Here there is an early notch superiorly with a disc hemorrhage. There is loss of the reflectance in the supero-temporal RNFL.

Retinal Nerve Fibre Layer (RNFL) defects are classically easiest to identify on a greyscale image with high contrast. Here there is a relatively narrow supero-temporal defect with early notch and hemorrhage.

2.1 Disc Rim Haemorrhage ("Drance" Haemorrhage)



a. What is disc rim haemorrhage?

Disc rim haemorrhages are splinter or flame-shaped haemorrhages, which usually traverse the disc margin, although they can be within half a disc diameter of the disc margin. Retinal haemorrhages further away from this suggest a primary vascular problem. They are often seen in eyes with glaucomatous damage and are commonly located in the infero-temporal or supero-temporal quadrants.[12] They are

usually seen in eyes with early to moderate damage. Their frequency decreases in eyes with advanced disease. Disc hemorrhages are important finding as often they are the first to appear in glaucomatous eyes preceding retinal nerve fiber layer defects, rim loss and visual field defects. Disc hemorrhages are not pathognomic of glaucoma and can be found in eyes with posterior vitreous detachment, optic drusens, anterior ischemic optic neuropathy and have many systemic associations.[13] The haemorrhages are more common in an area of instability, certainly at the edge of a pre-existing notch, but can be quite difficult to pick up particularly if they are between vessels or are quite thin and resemble a vessel except that there is no beginning or end.

b. How is it measured?

Disc hemorrhages are not measured, although usually marked on the disc examination sheet, or noted on a photograph, or hand drawn on an OCT to identify their place. Disc hemorrhages are best seen on disc photographs and clinical examination. Modern imaging techniques such as CSLO and OCT are not good at picking up disc hemorrhages. Therefore, clinical examination is very important. The detection of disc hemorrhages depends on method of examination, pupillary dilation, clarity of the ocular media, experience of the examiner and type of glaucoma. Therefore, the reported prevalence of disc hemorrhages varies greatly in different studies (1.9% - 30%).[14,15] Overall, the detection rate for disc hemorrhages is low at about 5% of glaucomatous eyes.

c. Why is it important?

Disc rim hemorrhages though not pathognomic, are a significant finding suggesting glaucoma. They have high specificity but are not very sensitive in picking up glaucoma due to low prevalence. Disc rim hemorrhages often precede other signs such a rim loss and RNFL defects, therefore, they are at times the first clue to the diagnosis. They are particularly suggestive of glaucoma in eyes with high IOP. Disc hemorrhages are often associated with progressive disc damage and field changes. In this context they may indicate progression, particularly if in an area of disc instability. Although it does not prove progression, it certainly heightens the awareness of the clinician to its possibility, and it is valuable to detect disc rim hemorrhages for that reason. Missing a disc rim hemorrhage has been shown to decrease the overall likelihood of glaucoma score and can make a focal neuroretinal rim defect less obvious and important.[1]

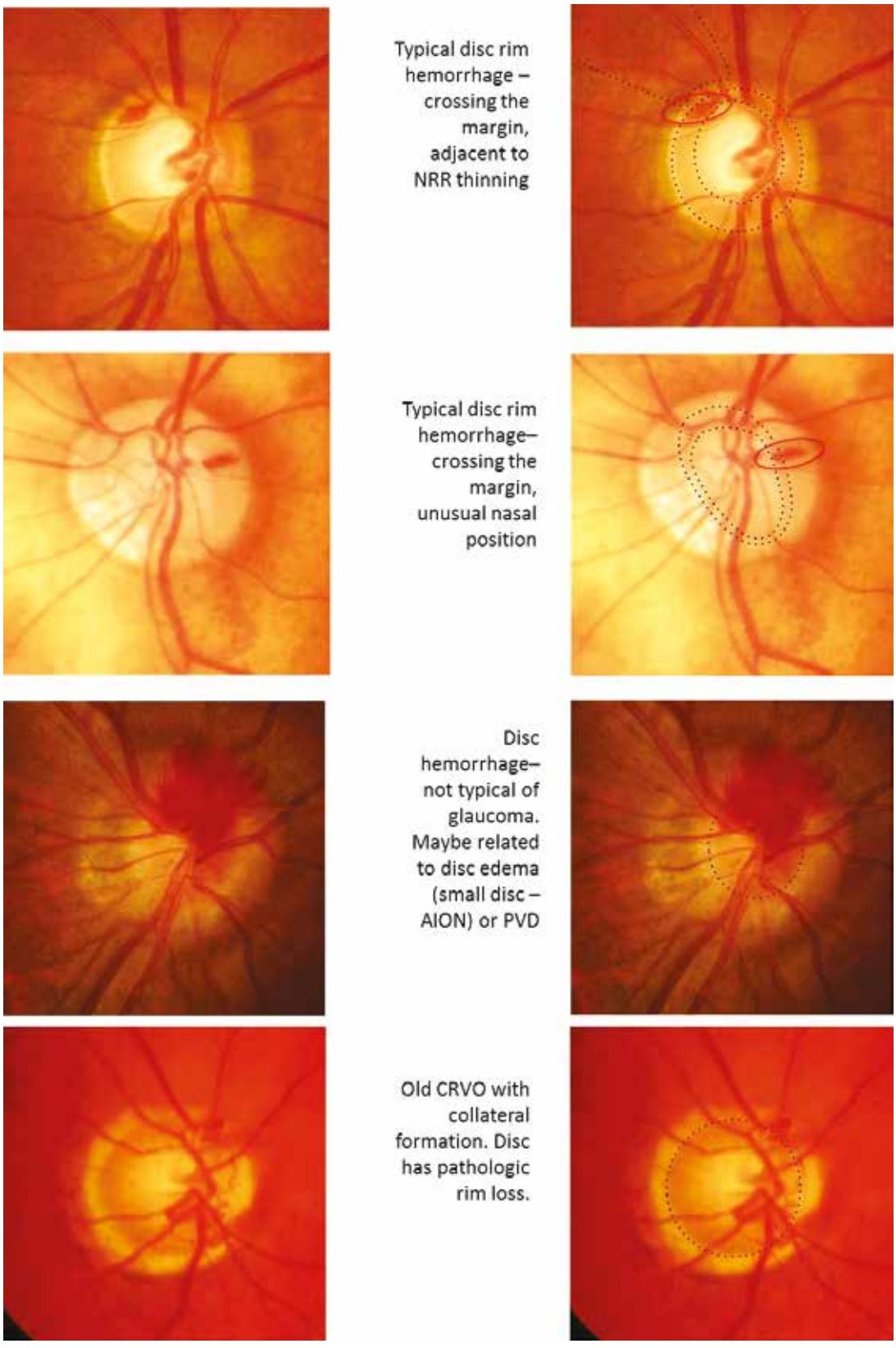
d. Background information

Disc rim hemorrhages in glaucomatous eyes were first noted by Bjerrum in 1889. Drance *et al.* in 1970s reemphasized association of disc hemorrhages in glaucoma and reported on their relationship with deterioration of visual fields. They were originally called splinter or flame-shaped hemorrhages, but their association with glaucoma was most eloquently described by Stephen Drance, hence they have been otherwise known as drance hemorrhages.[16]

The mechanism of disc hemorrhages remains controversial. Many investigators believe it to be due to vascular pathology as it is more often associated with normal tension glaucoma. While others believe that disc hemorrhages are due to structural changes in the optic nerve head induced by IOP. Higher IOP has been reported in eyes with disc hemorrhages than in eyes without them.

Disc rim hemorrhages can last many months, and some appear almost fixed in the tissue and others more ephemeral. Multiple and frequent disc rim hemorrhages in the same disc may suggest another pathology.

e. Examples



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Part - B

Non-Glaucomatous Optic Atrophy

Though the most common causes of optic neuropathy or atrophy is glaucoma, there are other non-glaucomatous optic neuropathies (NGON) that may have disc changes which are similar to glaucomatous optic atrophy (GON). Cupping has been classically described as a pathognomonic sign of glaucoma, however, NGONs can also present with an excavated disc. The differentiation of glaucomatous versus non-glaucomatous cupping can be challenging even for experienced clinicians.[1,2,3]

In eyes with GON neuro-retinal rim (NRR) loss occurs along with increased exposure of the lamina cribrosa. NRR loss predominantly occurs in the inferior and superior disc quadrants, and hence, cupping exhibits a vertical expansion. Damage to the laminar connective tissue due to ischemia causes loss of support leading to non-glaucomatous cupping secondary to optic nerve diseases and results in retrograde optic atrophy. This causes pre-laminar nerve fiber atrophy, post-laminar fibrosis, glial cell hyperplasia and posterior bowing of the lamina cribrosa.[4] Studies show that nearly 20% of patients with non-glaucomatous causes were misdiagnosed as glaucoma,[2,3] with compressive optic neuropathy as the most important diagnosis that was missed.

It is also important to remember that at times, the two entities may co-exist or one may develop subsequently independent of the other. A patient may have more than one disease which includes having a tumor in addition to glaucoma. Also, some of the hormone secreting pituitary adenomas may cause compressive damage causing field and disc changes and can also be corticosteroid hormone secreting and cause an endogenous steroid induced increase in intra-ocular pressure.

In this chapter, we highlight the clinical indicators of non-glaucomatous cupping and indications for neuro-imaging in glaucoma suspects.

Non-glaucomatous optic neuropathies mimicking glaucomatous disc changes

Several neuro-ophthalmic and retinal conditions lead to optic disc excavation and atrophy, and are frequently misdiagnosed as glaucoma, especially normal tension glaucoma.[1,2,3]

These neuro-ophthalmic disorders mimicking glaucoma are:

1. Congenital disc anomalies (disc coloboma; Figure 1)
2. Hereditary optic atrophy (Leber's, Autosomal dominant optic atrophy)
3. Toxic optic neuropathy (Methanol/ethambutol)
4. Intraorbital and intracranial mass lesions/chiasmal compression
5. Anterior and posterior ischemic optic neuropathy (both arteritic and non-arteritic)
6. Inflammatory and demyelinating optic neuritis
7. Cerebrovascular diseases
8. Radiation optic neuropathy
9. Carotid artery stenosis
10. Post-traumatic optic neuropathy

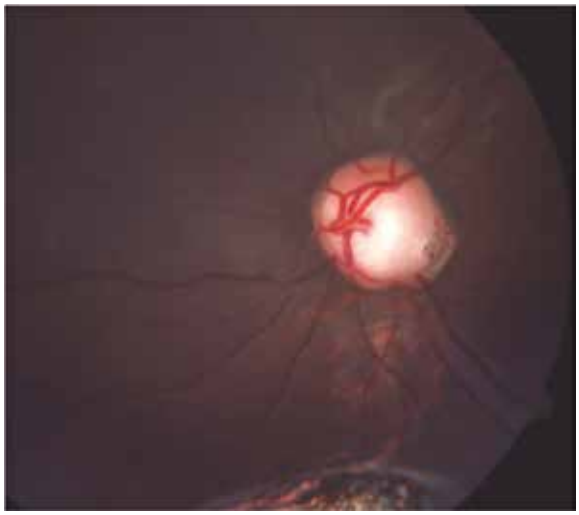

Figure 1: Optic disc coloboma

Differentiating glaucomatous and non-glaucomatous optic atrophy

A high index of suspicion is essential for diagnosing non-glaucomatous optic atrophy and a detailed history, clinical examination and appropriate investigations are important if there is a suspicion that glaucoma may not be the cause for the visual functional changes.

Differentiating points between GON and NGON

	Glaucomatous	Non-glaucomatous
Age	Mostly elderly	Any age group
Presenting complains	Mostly asymptomatic; except in advanced stage	Sudden onset decrease in visual functions
Visual acuity (VA)	Well preserved central vision until advanced stage	Early and severe vision loss
Colour vision	Not affected until advanced stage	Affected early
Pupils	No RAPD until advanced stage as relatively symmetrical disease	Often unilateral and asymmetrical involvement; RAPD present
Optic disc	Vertical cupping, splinter disc haemorrhages	NRR pallor>cupping
Visual field defects	Nasal step, arcuate defect, spares fixation until advanced stage	Central, centrocecal, altitudinal, bitemporal, hemianopic that respect vertical meridian

Demographics

Older patients[5,6,7] and female gender[8,9] are more likely to be glaucoma especially if there is a family history of glaucoma.[9] Age younger than 50 years is 93% specific for non-glaucomatous cupping.[3] However, these are soft indicators and must be interpreted in the light of clinical presentation.

Clinical presentation

For detecting optic nerve diseases, important tests include visual acuity testing, color vision assessment, stereoscopic optic nerve head assessment and visual field evaluation.

A detailed systemic history is important as NGON may be associated with neurologic and endocrine symptoms, e.g., headache, hypopituitarism, excessively high or low blood pressure, diabetes and abnormal diet. Prior episode of blood loss and major surgery may have caused post-surgical ischemic optic neuropathy which the patient may not associate with the visual loss.

Glaucomatous optic neuropathy tends to have significantly better visual acuity at presentation compared to NGON as the papillomacular bundle is the last to be affected in GON.[10] Glaucoma patients have a well preserved central visual acuity till advanced stage with visual field losses and optic disc cup changes appearing much earlier. NGON is more likely to present with loss of central acuity[11] and initial visual field changes, although having only mild changes in the optic cup.

Sudden decrease in vision/rapidly progressive vision loss is likely to be due to neuro-ophthalmological causes. Also note the speed of progression. Some neuro-ophthalmological

lesions progress more quickly than you would expect glaucoma to progress or would not show any change at all.

Other signs indicative of NGON are color vision abnormality and presence of a relative afferent pupillary defect (RAPD). RAPD detection in glaucoma patients is uncommon until in advanced stage. Therefore, RAPD in a patient having symmetric cupping should raise suspicion of NGON.

GON exhibits visual field defects that are bilateral though they may be asymmetrical, bordering the horizontal midline with NRR bundle defects unlike NGON that may present with field defects bordering the vertical midline. Nerve fiber bundle loss and arcuate defects may occur in both GON and NGON. However, certain field defects are extremely un-common in glaucoma eg, caecal and centrocaecal scotomas, hemianopic defects (chiasmal/ tract disease) and altitudinal defects (ischemic neuropathies). NGON may also present with non-specific field changes like diffuse depression, generalized constriction, blind spot enlargement, and central depression.[3] More than the type of field loss, GON shows a high correlation between the nerve fibes layer defects, the rim /disc changes and visual field defects[16,17] which is lacking in NGON. Also, patients with NGON have better visual field mean deviation (MD) and pattern standard deviation (PSD) compared to patients with GON. However, sometimes due to its subjective nature, field testing may be unreliable or highly variable and therefore may be misleading or not reflect the actual visual field defect.

Disc changes

Careful evaluation of the optic nerve head can help to differentiate glaucomatous cupping from non-glaucomatous cupping. In most cases, the optic disc rim thickness tends to follow the classical ISNT rule, i.e., NRR is broadest inferiorly, followed by superior, nasal and thinnest temporally. However, this rule might not hold true in cases of large optic discs. Disc cupping of more than 0.7 is infrequent in the general population and these cases need to be evaluated to rule out glaucoma. However, since small and large optic disc sizes may not follow the above principles, they pose a diagnostic difficulty and care must be taken while interpreting these discs. Small discs have almost no cup and visual field losses may have occurred before cupping can be detected. Hence, early glaucomatous damage may be overlooked in small optic discs. On the contrary, in large discs, a large cup is present often physiologically without glaucomatous damage or field loss. In such cases, detection of disc hemorrhages, parapapillary chorioretinal atrophy and observing the retinal nerve fibre layer becomes important to find genuine optic nerve damage. Also, the configuration of the NRR is to be looked at and checked for the ISNT rule. Bilaterally symmetrical, large cups may be physiological, or may also be associated with high myopia.

Features in favour of GON are focal NRR loss, vertical elongation of optic cup (preferential thinning of superior and inferior NRR), PPA and flame-shaped disc hemorrhages. These discs display focal or concentric enlargement with an increase of vertical diameter disproportionate to the horizontal. Glaucomatous cups also show deep excavation and wedge shaped nerve fiber layer defects.[12] In contrast, non-glaucomatous cupping shows diffuse rim thinning, although complete loss of the disc rim is rare. Moreover, in glaucomatous cupping there is a

good correlation between visual field defects and disc changes, but is not so consistent in non-glaucomatous disc changes.[13]

Another important feature apart from the thickness of the NRR is the color. A normal healthy optic disc rim is orange in colour, due to hue coming from capillaries. Pallor of the NRR,[3] diffuse or temporal loss of NRR[3] and pallor in excess of cupping[3] are features suggestive of non-glaucomatous cupping. Trobe et al,[14] identified NRR pallor to be 95% specific for non-glaucomatous cupping, while focal or diffuse obliteration of the NRR to be 87% specific for glaucomatous cupping. However, pallor is a relative finding and even with a preserved NRR, pallor may actually be very subtle. In cases of doubt the other eye disc may be used to compare for changes. Moreover, in presence of advanced cupping, pallor can no longer be considered an important differentiating sign.[15]

While elevated IOP with associated signs and symptoms is glaucoma, unless proved otherwise, single readings with moderately raised IOP should not be considered diagnostic. Reliable multiple readings are important to confirm the diagnosis of glaucoma.

Investigations

While a detailed history and clinical examination is key to the diagnosis of NGON, newer modalities using optical coherence tomography (OCT), scanning laser ophthalmoscopy (CSLO), etc can also help in doubtful cases.

Optical coherence tomography

Identification of optic nerve changes by looking at a clinical photograph is subjective. OCT can be useful in differentiating GON from NGON based on retinal nerve fiber (RNFL) thickness. Gupta *et al*[18] showed that patients with non-glaucomatous cupping have lower nasal and temporal RNFL thickness, as well as lower macular thickness and volume compared to patients with glaucomatous optic nerve cupping. Diffuse pattern of RNFL loss is generally suggestive of non-glaucomatous cupping with the RNFL loss not occuring focally in the superior and inferior quadrants, as seen in glaucoma. Histopathologically it has been demonstrated that RNFL loss in NGON occurs in a more varied manner depending on the etiology.[19,20] In glaucoma, RNFL loss has been seen to extend beyond the region corresponding to the visual field defect and may be of immense potential for early detection of glaucoma cases showing significant cupping, but no significant field defects.

Macular volume measurement also seems to be a better indicator for NGON. For similar average RNFL thickness, macular volume is found to be reduced significantly more in these patients. Specifically, compressive mass lesions have been shown to preferentially damage smaller macular fibers travelling in the optic nerve.[21] Also, a preferential damage to the papillo-macular bundle in NGON may also be the reason of reduced macular thickness and volume.

Enhanced depth imaging optical coherence tomography (EDI OCT) studies have found that measurement of the optic cup depths from the level of the Bruch's membrane (anterior laminar depth) may have a good ability to differentiate between glaucomatous versus non-glaucomatous

cupping.[22] The anterior laminar depth has been found significantly higher in glaucoma eyes therefore the 'deep' form of cupping is relatively specific to glaucoma.[23] In spite of the relative sensitivity of OCT in detection of RNFL thinning, diagnosis should rely on various parameters like patient history, visual field assessment and clinical data.

Neuroimaging

Neuroimaging of the visual pathways becomes important when we want to rule out the possibility of a compressive or a demyelinating lesion. Intracranial compressive lesions with compressive optic neuropathy can present with disc excavation, progressive field loss and can be confused with normal tension glaucoma (NTG). In such cases with diagnostic dilemma, contrast enhanced magnetic resonance imaging (CEMRI) of the brain and orbits are indicated. If affordability is a concern, then contrast enhanced computed tomography (CECT) of the head and orbits may be considered instead. Appropriate tests directed to pick up the suspected lesion and if required, interpretation of imaging in discussion with a radiologist is important so that subtle visual pathway involvement may be identified. Also the lesion should be able to explain the clinical presentation and incidental findings or artifacts should not confuse the diagnosis.

The following are some of the indications for neuro-imaging in atypical presentations of a case suspected to have a glaucomatous cupping:[24]

1. Young age (<50 years)
2. Lower levels of visual acuity (<20/40)
3. Vertically aligned visual field defects
4. Pallor of NRR
5. Shallow optic disc cupping
6. Asymmetrical loss of colour vision
7. Presence of RAPD

Summary

The diagnosis of glaucomatous versus non-glaucomatous optic neuropathy is often challenging even in the hands of experienced clinicians. Moreover both entities may co-exist or develop subsequently in a patient therefore a high index of suspicion is important. A thorough history and careful clinical evaluation is essential, especially if the presentation may not conform to the classical pattern of disc and visual functional changes or there are other systemic signs. Investigations like visual fields, optical coherence tomography and neuroimaging can help in confirming the diagnosis. Don't rely on a single piece of information. Therefore, it is crucial to keep an open mind while examining the patient, and to make a diagnosis in the light of all investigations. If the doubt still persists, it is best to follow the patient closely and not hesitate to seek a second opinion.

Case 1

A 47-year-old male patient presented with complaints of progressive increase in black spots in field of vision for the past 2 years. He was evaluated outside and diagnosed as having glaucoma with the baseline intraocular pressures of 24 mmHg OD and 23 mmHg OS, and was under treatment with beta blockers and alpha 2 agonists drops for the same for past two years.

On ocular examination, his best-corrected visual acuity bilaterally for distance and near was 6/6 and N6 respectively. His intraocular pressures were 16 mmHg bilaterally with a central corneal thickness of 590 microns OD and 603 microns OS. Fundus examination revealed asymmetric cupping of the disc with mild temporal pallor (right>left) (Figure 2). Visual fields revealed visual field defects involving the fixation (right>left) (Figure 3A & B).

An optic nerve OCT scan revealed a global RNFL thinning in RE with a infero-temporal RNFL thinning in OS (Figure 3C).

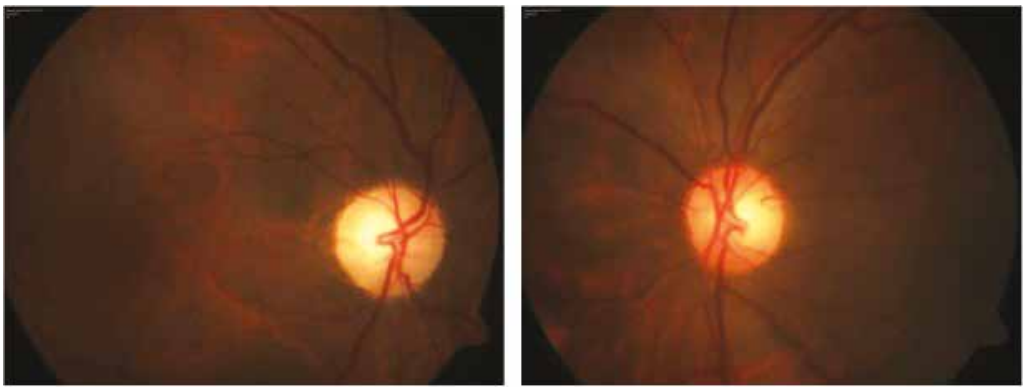

Figure 2: Right eye optic nerve with temporal pallor compared to left optic nerve.

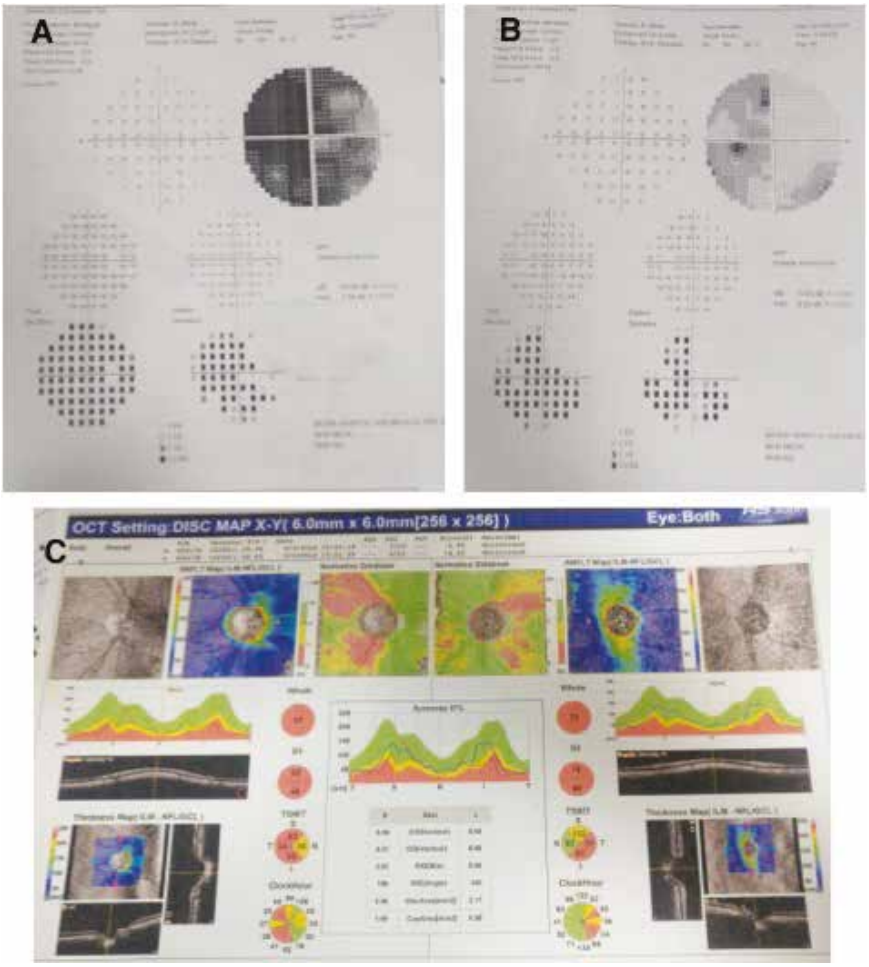

Figure 3: Visual fields and optic disc OCT of the patient.

Reconsider diagnosis of glaucoma:

1. Progressive gradual increase in field defects despite controlled IOP
2. Bilateral temporal disc pallor
3. Field defects respecting the vertical meridian and closer to fixation

CEMRI of the brain and orbits was ordered. Neuroimaging revealed 38 X 30 mm pituitary macroadenoma, extending to suprasellar space and encasing the right internal carotid artery (Figure 4). The patient was diagnosed as having bilateral optic neuropathy secondary to chiasmal compression due to large pituitary macroadenoma. The patient was urgently referred to neurosurgery for the management of the same.

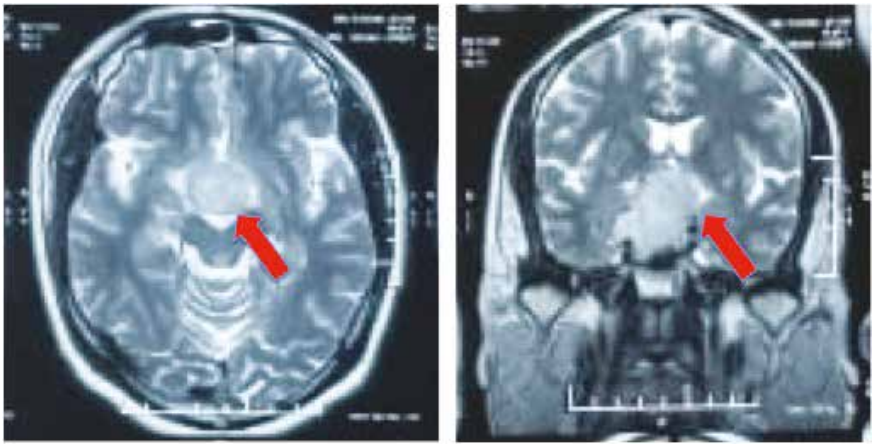

Figure 4: CEMRI of brain showing a pituitary macroadenoma (red arrow).

Case 2

A 19-year-old male patient presented with sudden onset diminution of vision that started 2 months back in the right eye followed by left eye with mild fluctuation in vision in between. He gave no history of tobacco or alcohol abuse or family history of glaucoma. His best-corrected visual acuity was 6/60 OD and 6/36 OS. Intraocular pressures were 16 mmHg bilaterally. In both eyes, the optic nerve head revealed a 0.9 cupping, with extensive NRR thinning and disc pallor (Figure 5). Perimetry revealed dense central scotomas in both eyes (Figure 6A & B). Neuroimaging was advised in view of bilateral progressive decline in vision and bilateral disc pallor. MRI brain revealed no abnormality in the central nervous system. Keeping the typical

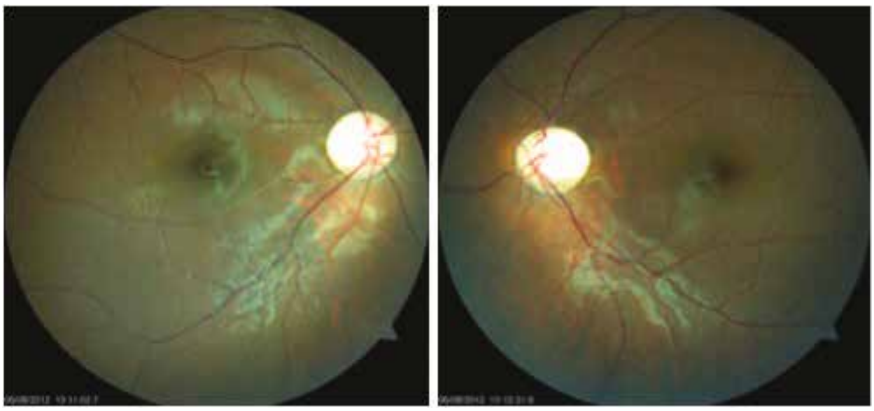

Figure 5: Fundus pictures of right and left eye showing NRR thinning and pallor.

history and central field defects in mind, a genetic analysis was sought that came positive for one of the primary mutations of Leber's Hereditary Optic Neuropathy (Figure 6C). Hence, a diagnosis was reached and patient was kept on multivitamin cocktail and followed up. Remember that cupping can be due to causes other than glaucoma.

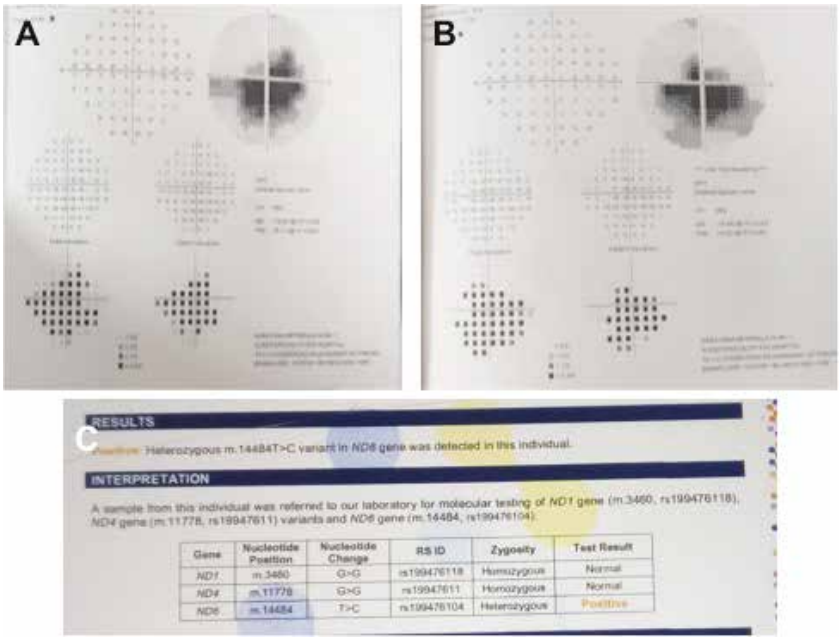

Figure 6: Perimetry showing central dense scotomas (A,B) and Genetic testing was positive for LHON (C).

Case 3

56-year-old male patient presented with sudden onset decrease in vision of left eye, 6 months back, noticed on waking up. He was a known diabetic and hypertensive. On examination, his BCVA was 2/60 OS; 6/6 OD with left eye RAPD. He had normal IOP in both eyes. His fundus picture, fields and OCT is given below (Figures 7, 8).

While early presentation may easily be diagnosed on the basis of absence of cupping but ischemic optic neuropathy is often confused with glaucoma in non-acute stage due to diffuse progressive excavation of the disc.

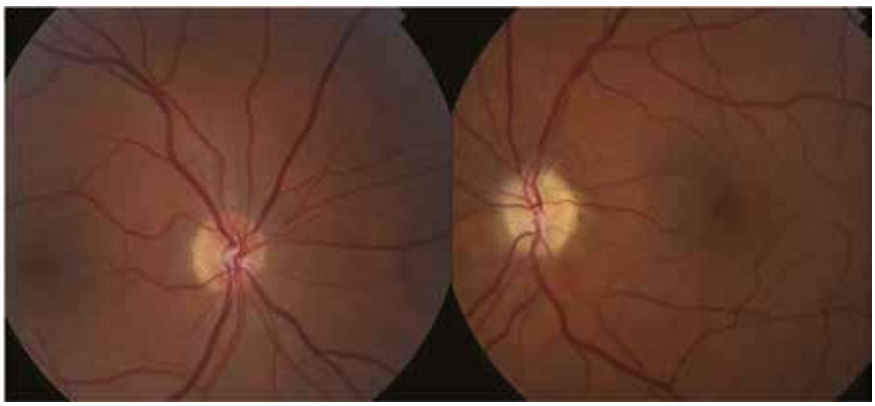

Figure 7: Fundus picture of right and left eyes showing absence of cup and pallor and mild blurring of ONH margins of left eye.

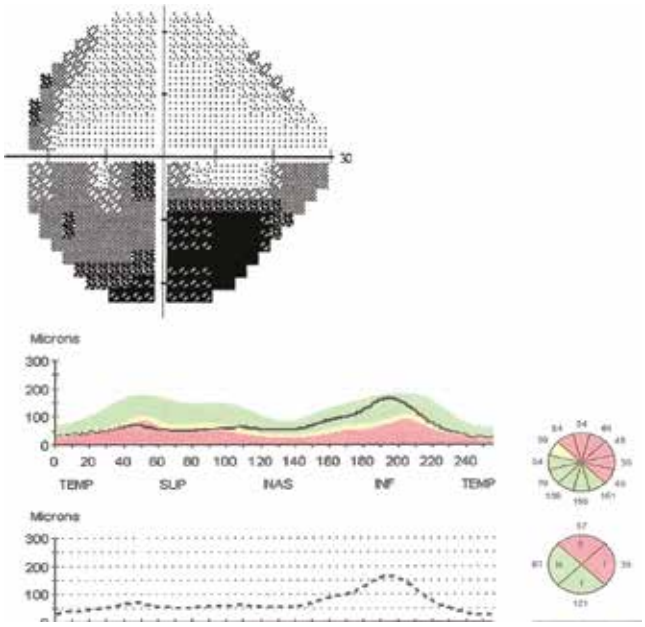

Figure 8: Inferior visual field and superior RNFL defects in left eye.

Optic disc cupping is seen in 14% cases of NAION and 92% cases of AAION[25] which is due to loss of disc substance caused by ischemia. This is often accompanied by marked focal arterial narrowing near the disc.

Features helping in ruling out glaucoma are:

- Cupping is diffuse, not focal with generalized/ sectoral disc pallor (Figure 8: superior sector involvement)
- Associated features of arteritic ischemic neuropathy may be present- headache, jaw claudication, weight loss, fever
- Sudden onset, severe vision loss
- Absence of progression
- Visual field defect involving the fixation
- Small crowded disc in the fellow eye; "disc at risk"

Case 4

A 45-year-old man presented with progressive vision loss in the left eye. He had counting fingers close to face in left eye with 20/20 acuity in the right with a left RAPD. The fundus examination (Figure 9) revealed an increased cup-to-disc ratio with pallor of the left disc and a normal optic nerve on the right. Visual field examination of the right eye showed a superior temporal defect (Figure 10). Left eye field was not possible due to poor vision.

As the right eye disc was normal, such a field defect was unlikely in glaucoma. It is possible in presence of a compressive lesion in the area of the chiasma. A lesion that is located anteriorly compressing the medial aspect of the junction between the chiasm and the optic nerve will affect the ipsilateral optic nerve fibers and the contralateral fibers of Willebrand knee (the crossing of the temporal retinal fibers). This results in ipsilateral vision loss and contralateral superior temporal field defect (Junctional scotoma or anterior chiasmal syndrome).

In this patient, the relatively young age, the asymmetric involvement, the visual field pattern and the optic nerve appearance prompted imaging.

Imaging confirmed the presence of an intra-cranial mass.

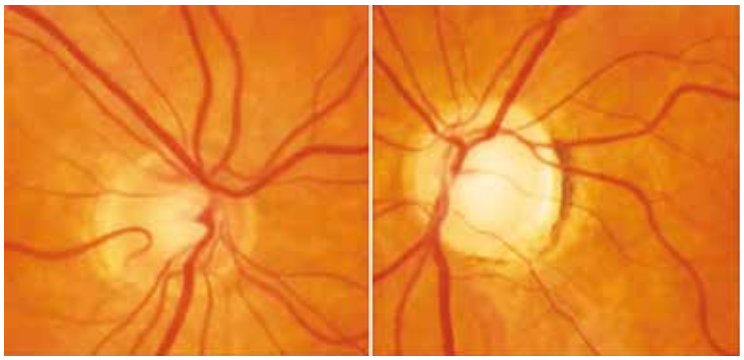

Figure 9: Increased CDR with pallor in left eye.

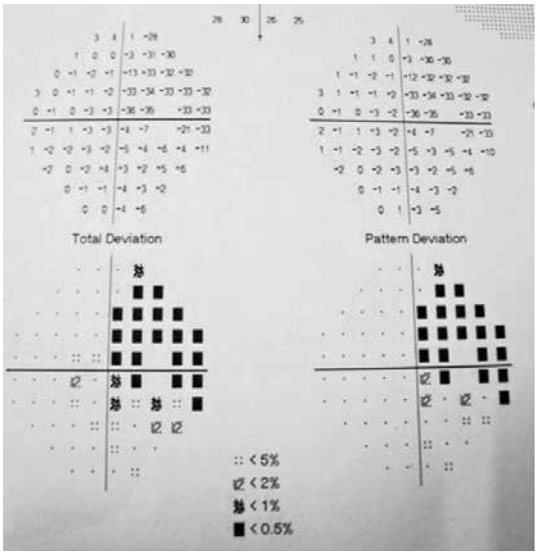

Figure 10: Right eye visual field showing superior temporal defect.

Case 5:

A 34-year-old male presented with recurrent episodes of decrease in vision in both eyes for past 3 years. There was partial recovery in vision after each episode. He was on treatment with oral steroids intermittently whenever his vision had deteriorated and topical anti-glaucoma medication due to suspicion of Juvenile glaucoma due to fundus picture (Figure 11), although his IOP had never been recorded high.

He tested positive for neuro-myelitis optica (AQP4 antibodies) and was started on Azathioprine and the anti-glaucoma medications were stopped.

As over time, NMO can present with disc excavation, the anti-glaucoma treatment was stopped.

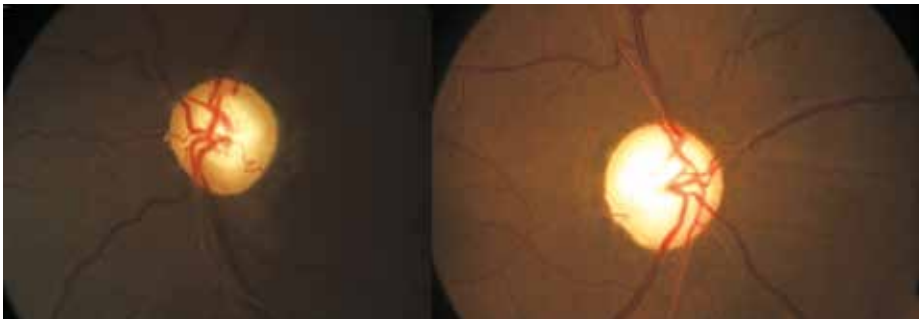

Figure 11: Increased CDR with pallor in right and left optic nerves.

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Annexure - II

IMAGING WITH A SMART PHONE

Smartphone-based ocular imaging can be of immense help in the subspecialty of glaucoma. Anterior segment imaging, assessment and documentation can be fairly performed with the existing optics of various smartphones. Here, we discuss few methods from a glaucoma perspective.

Anterior segment photography

Changes along the iris, the anterior chamber angle and the anterior chamber depth can be imaged using smartphone along with a simple magnifying 10x lens called "macro lens". The macro lens is clipped along the smartphone camera and photographs are taken using the method described below. (Figure 1A,B)

Figure 1: (A) Macro lens with a customized clip. **(B)** Macro lens with the clip attached on the smartphone.

First, the subject/patient is made to sit on a chair comfortably and requested to position his/her head straight. An observer sits opposite to subject/patient and takes forward the macro lens clipped smartphone gradually towards the eye. A video mode or a standstill photo mode can be selected. However, video mode is preferred as it provides a continuous light source. At a distance of 3 cm to 5 cm from the ocular surface, a clear image can be appreciated on the smartphone screen. (Figure 2A) If required, any part of the screen can be manually tapped to focus clearly on any tissue of interest including cornea, iris and the lens (Figure 2B).

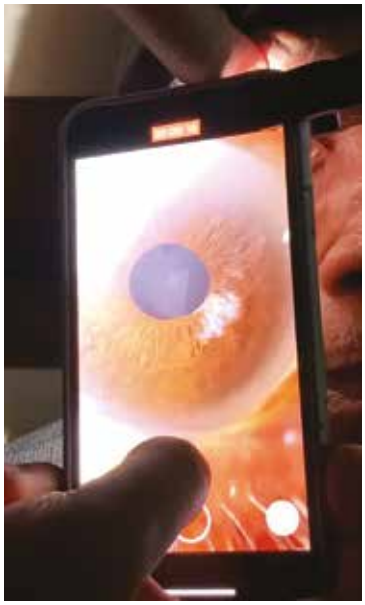


Figure 2A: External photograph showing the position of patient and the macro lens clipped smartphone.

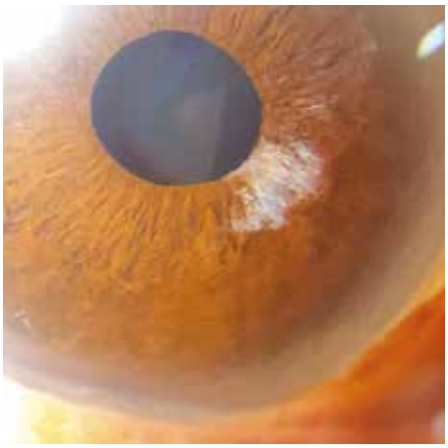


Figure 2B: Image acquired by the smartphone.

Angle video documentation and still photography

Patient is made to sit on a chair and his head is firmly placed against a wall. This procedure requires two observers. First, place the Goldmann 4 mirror gonioscope on the cornea of the patient and simultaneously project a thin slit beam of a direct ophthalmoscope along the gonioscope surface to simulate a slit lamp beam. Then the other observer takes the photograph using the macro lens attached smart phone. Here we choose iPhone 11 pro max as it possesses 4K video recording facility (Apple inclusive California, no financial interests). In this phone, a wide-angle camera mode is chosen (1x mode) and under this, the video magnification is increased to 3x. The central square of autofocus is tapped along the angle structures and when a clear angle image noticed recording is initiated. The inferior and superior angle details were clearly recorded in various cases. During the video recording, standstill images can also be obtained without switching the mode. (Figure 3) However, it needs practice as the hands of the observer are not supported anywhere.

Figure 3: External photograph detailing the gonioscope held over the eye by the left hand of first observer and with the right hand a streak light from the direct ophthalmoscope is projected onto the gonio mirror. The second observer from the side acquires the angle images/ videos using smartphone clipped with macro lens.

Optic disc imaging

Direct optic disc imaging can be acquired using the iPhone X. (Apple inclusive California, no financial interests). The smartphone camera application is opened and a video mode with continuous flash light source is selected, now the smartphone is held with both the hands and slowly advanced towards the patient's eye. The central screen area is tapped to focus on the area of interest and the disc, its cupping, rim health and colour, rim thickness, peripapillary area, and the retinal nerve fibre layer can be very well appreciated. In addition, these videos are easily stored in smartphones as well as in other electronic devices such as laptops and electronic accounts (email and cloud accounts) for subsequent analysis and comparison. (Figure 4A, B).

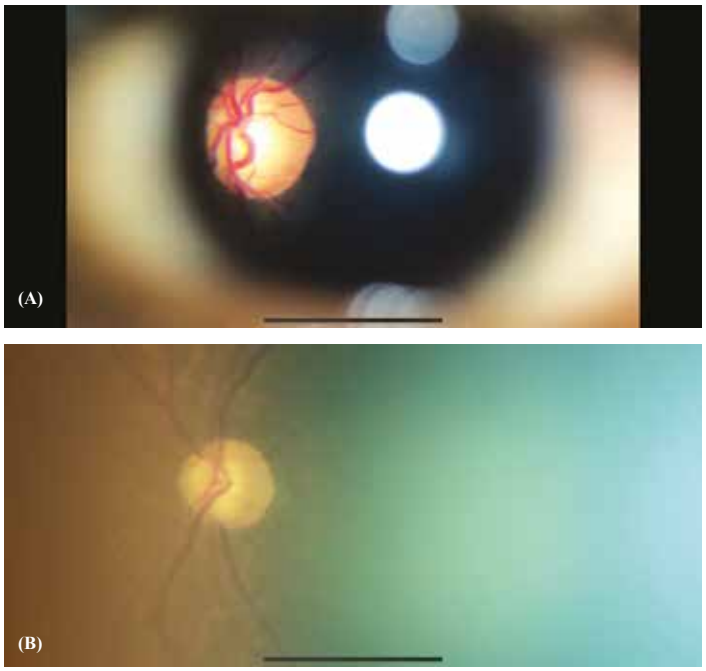
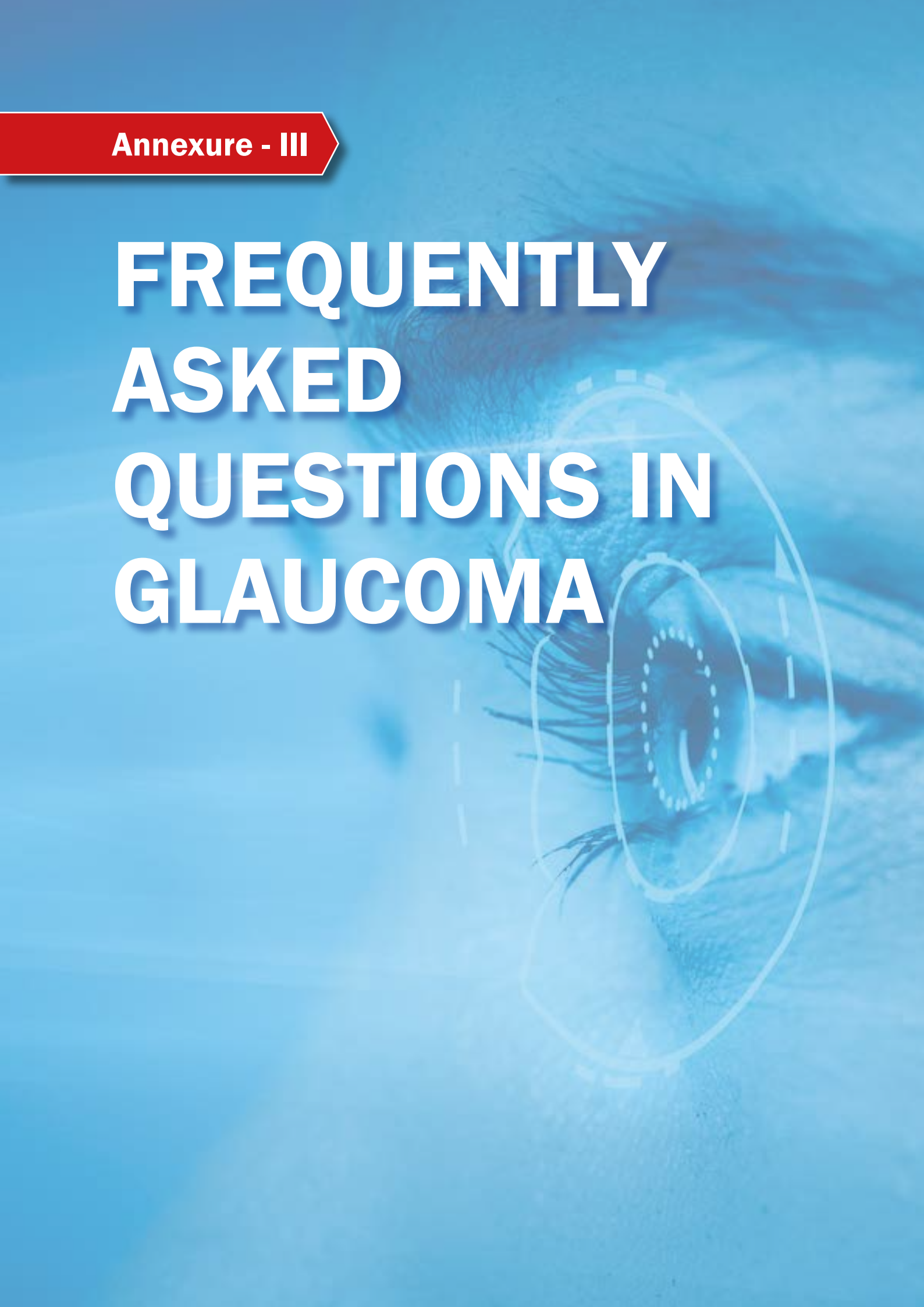


Figure 4 (A, B): Direct iPhone X acquired optic disc image in glaucomatous patients.

Annexure - III

FREQUENTLY ASKED QUESTIONS IN GLAUCOMA



1. **Which tonometer is the gold standard for IOP measurement?**

   Goldmann applanation tonometer (GAT). Glaucoma treatment is life-long and IOP should be confirmed by taking 2-3 readings with GAT at different time points in the day before starting therapy. Treatment should not be started based on high IOP readings on NCT.

2. **What is the importance of 520 microns with regards to central corneal thickness (CCT) and IOP estimation with applanation tonometer?**

   The CCT of 520 µm is important, because, Goldmann and Schmidt built the applanation tonometer with the assumption that the CCT was constant and calibrated the tonometer for a mean CCT of 520 µm. Hence, the IOP recorded would be inaccurate in corneas differing from that value.

3. **How to measure IOP post-refractive surgery?**

   - Laser refractive surgery reshapes the central cornea with deepest part of ablation at the center. The decrease in CCT post refractive surgery and altered biomechanics (corneal hysteresis) leads to underestimation of IOP and no tonometer is perfect for this.
   - GAT can be used in these eyes with the understanding that post LASIK eyes have thinner cornea and hence possibility of under-estimation of IOP. The baseline IOP can be evaluated before and 3 months after surgery.
   - Dynamic contour tonometry can be used as it measures transcorneal pressure with minimal deformation of the cornea, possibly independent of corneal thickness and rigidity.
   - Tonopen reading is to be taken in the peripheral cornea outside the corneal flap area pre- and post-surgery, especially in conditions where interface fluid is suspected. However, this measurement is only an approximation.

4. **What is Normal IOP and Target IOP?**

   "Normal" IOP is a statistical description of the range of IOP in the population.

   At birth, IOP is 6-8 mmHg

   At 12 years, it is 12 ± 3 mmHg

   In adults, it is 16 ± 2 SD (which is 21 mmHg)

   Target IOP:

   - The highest IOP in a given eye at which no clinically apparent nerve damage occurs
   - The IOP at which the rate of ganglion cell loss = the age dependent loss
   - As a very general rule, IOP should always be less than 18 mmHg in any glaucoma patient at any time point.

5. **How do you estimate target IOP?**

   This is estimated by assessing the severity of optic nerve damage and speed of progression. Other factors that are considered are -

   - Optic Disc damage at the time of assessing the target IOP
   - Existing visual field loss
   - Baseline IOP or IOP at which the damage occurred
   - Age of the patient (Life expectancy).

- Consider local and systemic factors (one eyed, vascular occlusion, central corneal thickness, pseudoexfoliation, family history, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, etc.)

6. Can target IOP vary from time to time?

Yes, based on the disease stability. If progression is noted on previously set target IOP, it should be reset to a lower value after ensuring adequate compliance. In an elderly patient with no progression over long term follow-up, it may be reset at a higher value, especially if drug related side effects are impacting quality of life.

7. Do we need to perform gonioscopy in eyes with deep anterior chamber?

We should perform gonioscopy at the time of diagnosis in all patients irrespective of the anterior chamber depth. Gonioscopy can also be performed even if the pupil is dilated. A open angle despite pupillary dilation rules out possibility of angle closure. However, in case of closed angles or narrow opening, angle status can be confirmed by repeating gonioscopy in undilated pupil.

It is not uncommon to see closed angles in eyes with central deep anterior chamber. Not performing gonioscopy and missing irido-trabecular adhesions is a critical error.

8. Should gonioscopy be repeated in POAG patients?

With advancing age, angle closure component may develop because of increasing thickness of lens, which may warrant peripheral iridotomy to prevent pupillary block. Hence gonioscopy should be done annually in phakic POAG patients.

9. Can IOP be the only Criterion to start treatment?

Disc and NFL damage rather than IOP is the criteria for starting medical treatment. However, in the setting of IOP > 30 mmHg with normal disc and RNFL, with normal or lower CCT, especially in older patients, it would be better to start treatment with one medication to prevent risk of vascular occlusions.

10. Is there a role of topical steroids in the preoperative period if patient is not medically controlled and scheduled for trabeculectomy?

Topical steroids can be started 2-4 weeks before surgery to reduce conjunctival inflammation caused by multiple topical medications. However, there can be rise in IOP and oral acetazolamide may have to prescribed. IOP needs to be closely monitored.

11. What is the role of SLT in POAG?

SLT has a role in the management of POAG, especially in OHT and early glaucoma. It is more effective in treatment naïve eyes. Short-term IOP spikes in a small percentage should be taken into consideration when it is advised. However, the effect of the laser wanes off over time, and patients need to be followed-up on a regular basis.

12. What advice should you give to the patient after prescribing therapy?

Always put only one eye drop at the prescribed time keeping an alarm on your mobile phone, never touch bottle nozzle to conjunctiva, occlude punctum with digital pressure for

1 minute after putting the eye drop and clean any excess drop falling over the periorbital skin.

13. What are the non-glaucomatous conditions with acquired cupping mimicking POAG?

- Chiasmal compression
- AION
- Toxic optic neuropathies, especially drug induced
- Hypotension (shock optic neuropathy)
- Hereditary optic neuropathies such as LHON.

14. What systemic co-morbidities and drugs are to be considered before we start Glaucoma treatment?

Asthma, heart block, hypertension on beta blockers, hypotension, diabetes mellitus, thyroid eye disease, cerebrovascular disease, sleep apnea, migraine, renal condition (serum urea and creatinine), arthritis, prostrate hypertrophy (drugs), myasthenia gravis, MAO inhibitors, antidepressants, parkinsonism, sulfa drug allergy, vasospastic conditions, etc.

15. What is MRMT – Maximum Reasonable Medical Treatment?

Maximum Reasonable Medical Treatment or Optimal medical therapy generally includes three to four medications in no more than two bottles. It has replaced the concept of maximal medical therapy. Adding a fourth medication gives an additional drop of IOP of < 15% most of the time. At this stage, patient should be counseled for surgery if target IOP is not achieved.

Example: Prostaglandin + Timolol combination once-a-day in the morning along with Brimonidine + Brinzolamide combination twice-a-day.

16. What is the drug of choice as the 1st line of treatment of glaucoma patients?

Prostaglandin analogues (PGA) (Latanoprost, Travoprost, Bimatoprost and Tafluoprost). Preservative-free drugs (esp. BAC-free) are ideal to decrease ocular surface disease. Low cost and high quality generic PGA drugs are available in India and should be preferred over beta blockers which have systemic side effects.

17. How can we help improve patient adherence or persistence to medical treatment?

- Involve the family and educate them about the disease.
- Emphasize the need for life long follow-up and treatment.
- Explain about the aim of therapy to prevent disease progression and blindness and not to reverse visual loss.
- Explain about side effects of treatment (Refer to AIOS Public Education Booklet).

18. How important is family history of glaucoma?

Around half of all POAG patients have a positive family history, and their first degree relatives (parents, siblings or children) have an approximately 10 fold increased risk of developing glaucoma. Once you diagnose a family member with glaucoma, screen the entire family annually, especially above the age of 40 years.

19. How do we treat patients with allergy to anti-glaucoma medications?

Drug-induced allergy (to AGM) is the closest differential diagnosis of a glaucoma patient on medical therapy presenting with follicular conjunctivitis/periocular blepharitis/ pseudomembranous conjunctivitis. Brimonidine is the most common offender. The drug should be withdrawn, and supportive therapy with topical low potency steroids and lubricants should be started. If needed, oral CAIs may be added to control IOP till allergy subsides.

20. What is the drug that can be safely used in pregnancy and lactation?

In the first trimester, teratogenicity is the major concern; in third trimester, pre-mature labour and during postpartum & lactation, secretion of the drug in breast milk and toxicity to the infant is a big concern. Juvenile glaucoma patients on medical therapy should be counseled to undergo surgery before conception. SLT can be performed. Try and avoid all drugs in first trimester. Brimonidine is the safest drug followed by PGA and beta blockers.

21. How often would you ask for visual fields in a POAG patient?

Once the diagnosis has been confirmed with reliable visual fields performed twice at baseline, the field should be tested every 4-6 months in newly diagnosed patients to check for progression (rapid versus slow) and on an annual basis thereafter if the disease is stable.

22. Do POAG patients need to get OCT done?

No, documentation of the optic disc with serial photographs on a biannual/annual basis is recommended. The OCT (with a high quality score/signal strength and interpreted by an expert) can be helpful in decision making if the physician is in doubt about diagnosis or progression of disease. Never start therapy based on an abnormal OCT alone.

23. Do you need to stop PG analogues before or after cataract surgery?

No need to stop PGA before surgery but stop after surgery for 6-8 weeks and then resume. Use any other class of drugs for 6 weeks.

24. Role of Citicoline or any other neuroprotective agent in the management of NTG?

Currently, there is no scientifically proven role of Citicoline or any other drug for neuro-protection in POAG patients.

25. When do we need to perform a diurnal check of IOP at multiple time points including night time and early morning?

- In patients with progressive glaucoma despite well controlled office IOP and good compliance.
- As a baseline in NTG patients to understand the baseline IOP, fluctuations, peak and trough IOP along with blood pressure monitoring.

26. Any Life style changes that may be beneficial in POAG?

Do regular aerobic exercises and consume a diet rich in fruits and raw vegetables. Meditation and slow breathing exercises can lower IOP levels and reduce stress associated with the disease. Patients with significant visual field defects should not drive as they are at increased risk of motor vehicle accidents due to their own fault.

Notes

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