INDIAN NEURO-OPHTHALMOLOGY SOCIETY
INOS TIMES
Volume 1 Issue 2 | April - June 2020

Annual Conference of INOS 2020 Stands Cancelled

From the desk of Secretary

Dear Friends and Colleagues,

We all are in the midst of a global pandemic which does not seem to end soon. I hope you all are safe and healthy. Like every other conference scheduled for this year, the 3rd Annual Conference of INOS has also become a casualty. It is with a deep sense of regret that I wish to inform you all that we have decided to cancel the annual conference that was supposed to be held on 29-30th August 2020. This was done considering the very difficult current situation caused by the COVID-19 worldwide and as the safety and health of our delegates has always been our top priority.

The next INOS Annual conference will be held next year when you will be able to concentrate on scientific matters and can spend some leisure time too. Information and registration regarding INOS 2021 will be circulated soon. We remain excited to host you then and will certainly keep you posted of our conference update through our website, emails, newsletters, and social media.

However that does not stop us from continuing our efforts to take Neuro-ophthalmology forward in India. The launch of INOS times was one such endeavor and we continue the same with 2nd issue of this year.

This issue promises to be as interesting as previous with two review articles and update on revised TB regimen. Resident corner this time is an interesting cross word and so is the case of the quarter. I hope this issue will keep readers engaged during these challenging times.

I would also like to invite readers to submit their research, cases, and reviews for the next issue. The readers can email their articles to ***secretariat.inos@gmail.com***

Stay Safe!!!

Best Regards,

Rohit Saxena
Secretary INOS

The Online World

Dear Friends,

With increasing counts of Covid cases in the country and the reluctance of patients to visit ophthalmology OPDs; Remote Teleneuro-ophthalmology Consultation via messaging apps has provided a temporary but useful alternative. Remote vision apps, colour vision apps, photographs of the individual eyes and videography of eye movements with smartphones along with the images of previous documents have simplified online neuro-ophthalmic consultation. However, the limiting factors are intraocular pressure measurement and self-fundus photography with smartphones. Software experts might come up with innovations for these too.

Deepak Mishra et al in the June issue of IJO reported a survey about the effect of the lockdown on ophthalmology training programs, both residency and fellowships, in India. It concluded that 75.7% (542/716) of the respondents felt that online classes and webinars were useful during the lockdown period. Dr. Santosh Honavar, in his editorial in the same issue, said that online teaching and assessment is the New Normal.

The INOS Times is an effort to periodically circulate practice oriented scientific content in Neuro-ophthalmology to our readers through the electronic medium. We sincerely hope readers would gain practical concepts and at the same time share interesting cases with the ophthalmic community via the INOS times. Contributions are welcome from each and everyone.

In the current issue, we have two reviews, one explaining how assessment of the ganglion cell layer- inner plexiform layer complex on OCT is a useful tool in the Neuro-ophthalmology clinic and another on the new developments in the medical management of thyroid associated ophthalmopathy. We also have an update on the rising tide in Ethambutol induced optic neuropathy, noticed in the past 2-3 years.

Here's wishing you happy reading and hoping all of us successfully reboot to the newer version of Ophthalmology, 2.0.

Looking forward to your feedback.

Satya Karna

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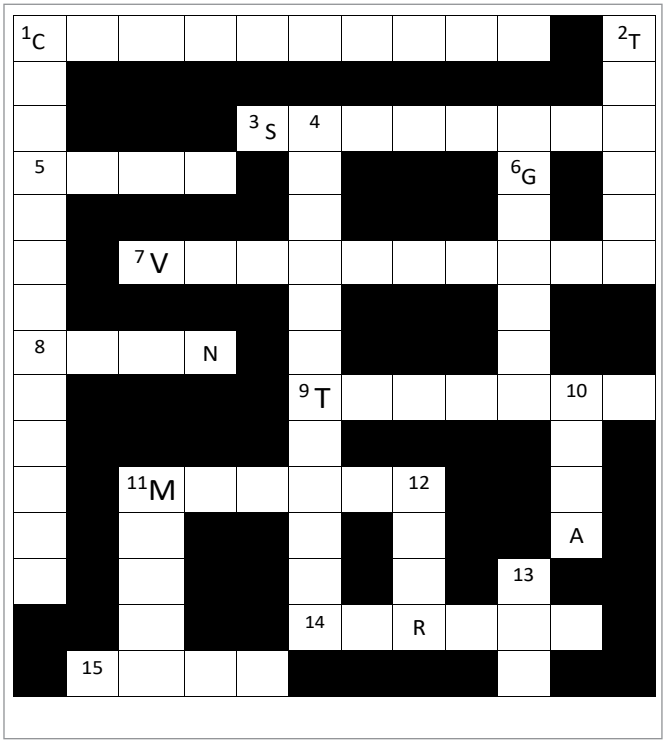
Resident Corner
Crossword

Sabyasachi Chakrabarty, Anurag Gandhi, Padmavathy Maharajan Hospital, Aravind Eye Hospital Madurai



ACROSS

1. You get me when yo ur favourite pet bites you. I am notorious for burning your optic nerve and retina together.

3. I am rare but relentless. Once you get me you turn blind and die within a few years.

5. I am a familial disease that causes your optic nerves to shrink and your eyes to shake. I do not affect your ears but you will find difficulty balancing.

7. You take me to cure a 'West'. But I can affect your nasal fields.

8. I have two circles in my name and one has blood in it.

9. You look to the sides and I make your pupils shrink. I am _____ phenomenon.

11. I am a congenital disease. I affect a lot of your cranial nerves and leave you expressionless.

14. I produce anisocoria. I may be seen when you have a non small cell lung cancer.

15. I was a chart created by a noble laureate who shares his middle name with Santa Claus's red-nosed reindeer.

DOWN

1. I treat neuralgic pain, but I can "beat" you "down".

2. I produce all forms of intraocular bleed when vessels burst inside your skull.

4. I am a sign of neuromuscular junction disorder

6. I am a syndrome where all cranial nerves are affected secondary to a tumour in the skull base.

10. I am a premonition.

11. I cause spasms in your eyes, face and neck. Which syndrome am I?

12 I am a sequence used to image the intraorbital optic nerve.

13. I am quite flashy. Check mate!

Answers are given on page no. 22

Sabyasachi Chakrabarty

Review

New Developments in the Medical Management of Thyroid Associated Ophthalmopathy

Pratibha Panmand, Ajay Krishnamurthy, Jyoti Matalia, Narayana Nethralaya, Bangalore

Thyroid associated ophthalmopathy (TAO) is a complex autoimmune manifestation of Graves' disease. Of late, TAO has been described along with other thyroid states such as Hashimoto's (3%), hypothyroidism (1%) and as well as in Euthyroid (6%) states.[1] The systemic thyroid abnormality and TAO run a parallel course and may not have any relation to its individual progression. About 40% of patients with Graves' disease develop clinically significant TAO.[2]

The symptoms of TAO can range from dry eyes to severe sight-threatening conditions such as exposure keratopathy and optic nerve compression. Patients more often are psychosocially affected because of the facial disfigurement resulting from proptosis, congestion, lid retraction and squinting. The disease progresses through two phases; active phase spanning for a period of 1-3 years followed by quiescent phase.[3] The treatment is most effective if it is given during the early active phase.

TAO has been through several promising and translational changes in the treatment, ranging from simple cessation of smoking to use of steroids or use of immunosuppressive drugs and to surgical management. Several clinical trials have been done in the past, but a robust treatment protocol for TAO is still lacking.

During the active phase of disease, it is prudent to curtail the disease with medical management and resorting to surgery if the need arises. Clinical trial of high-dose glucocorticoids with or without radiotherapy reduces inflammation related signs and symptoms of active thyroid ophthalmopathy, however it has very minimal effect on the proptosis and cannot be used for sustained maintenance in case of clinically active cases.[4]

Immunotherapies based on monoclonal antibodies against B cell surface antigen CD20, such as Rituximab, were suggested to benefit in decreasing orbital inflammation in patients with TAO. However, RCT of RTX demonstrated no therapeutic benefit over the placebo in patients with active and moderate to severe Graves' Orbitopathy.[5]

Advantages and disadvantages of drugs commonly used in Thyroid eye disease

	Advantages	**Disadvantages**
Glucocorticoids	Helpful in active thyroid eye disease	Minimal effect on proptosis and sustained maintenance
Azathioprine	Helpful in combination with Steroids	Liver toxicity
Cyclosporine	Steroid sparing effect	Gingival hyperplasia and Hypertension
Rituximab	Improves proptosis and lid retraction	High cost and potential toxicity

Immunoglobulins which activate IGF-1-R (Insulin like growth factor - Receptor) signaling are detected in patients with Grave' disease. Thyrotropin combines with IGF-1-R to form a signaling complex, this complex is over expressed by the orbital fibroblasts, T-cells and B-cells in Grave's disease and is further transactivated.[6] In orbital pre-adipocyte fibroblasts, IL-6 increases expression of the thyrotropin receptor, and the orbital volume is relative to IL-6 mRNA expression. Therefore, IL-6 may have several roles in the pathogenesis of TAO.

Tocilizumab has been used in successfully treating IL-6 associated rheumatoid arthritis. Since the effect of IL-6 is implicated in TAO as well, Perez-Moreiras et al.[7] studied the effect of Tocilizumab on moderate-severe corticosteroid resistant TAO. They found it to reduce clinical activity scores (CAS) by at least 2 in the 87% of drug group compared with 59% in the control group at week 40. Though the overall activity of the disease decreased at 40 weeks, there was no change in the exophthalmos. In a previous similar study by the same author,[8] there was improvement in the CAS (mean of 5.89) and reduction in the exophthalmos with the same drug. The differences between the two studies may be attributed to the confounding factor being the severity of the disease.

Few in-vitro studies have stated that IGF-IR–inhibitory antibodies presenting orbital fibroblasts and fibrocytes can attenuate the actions of IGF-I, thyrotropin, thyroid-stimulating immunoglobulins, and immunoglobulins isolated from patients with Graves' disease. These breakthrough findings have paved the way for trial of teprotumumab a IGF-IR inhibitory monoclonal antibody to be used in patients with active, moderate-to-severe ophthalmopathy.[9,10]

Recently based on 2 studies, [11, 12] teprotumumab has been approved by FDA, which has brought in a breakthrough change in the treatment of this potentially debilitating disease. This approval is based on the results of multicenter, double-masked, placebo-controlled study carried out on 87 patients diagnosed with active thyroid disease though 88 were recruited. Patient were randomized to receive either the drug or the placebo administered IV infusion over a period of 24 weeks for a total of 8 infusions. Initial starting dose is 10 mg/kg, later titrated to 20 mg/kg and then was kept constant for the duration of the study.[11] Of the 87 patients, 42 were in the teprotumumab group and 42 in the placebo group. A total of 39 patients in the placebo group (87%) and 37 patients in the teprotumumab group (88%) completed the intervention.[11] In the intention-to-treat population, 29 of 42 patients who received teprotumumab (69%), as compared with 9 of 45 patients who received placebo (20%), had a response at week 24 (adjusted odds ratio, 8.86; $P<0.001$). In the active thyroid group, at the end of 24 weeks, 40% patients in the teprotumumab group has reduction of 4 mm or more of the proptosis but no reduction was noted in the placebo group. The CAS significantly reduced in the teprotumumab group compared to the placebo. At 24 weeks, 69% of the teprotumumab group had a CAS of 0 points or 1 point, compared with 21% of patients who received placebo. The GO-QOL[13] visual functioning score had significantly increased from 12.8 to 15.6 points greater than the increase in the placebo group. The response rate with respect to subjective diplopia was significantly higher in the teprotumumab group as compared to the placebo.

Hyperglycemia was the only adverse event which was identified being related to the drug teprotumumab, which was monitored with blood glucose and glycated hemoglobin levels and was very well controlled with medications. Serious adverse events like diarrhea, inflammatory bowel disease, Escherichia sepsis, Hashimoto's encephalopathy, urinary retention occurred in 12% of the teprotumumab group and 2% of the placebo group had only optic neuropathy, however these were not related to the drug.[11]

Similarly, the other study[12] concluded that teprotumumab resulted in better outcomes with respect to proptosis, CAS, diplopia, and quality of

life than placebo with uncommon serious adverse events among patients with active thyroid eye disease. Effectiveness of the drug teprotumumab during the inactive phase is still yet to be determined.[12]

However, in hindsight, we cannot disregard the studies where they have observed circulating antibodies to the IGF-IR which are unlikely to be a helpful biomarker as they are found only in a fourth of Grave' patients and regardless of whether thyroid eye disease is present.[14]

Since the study based on teprotumumab was placebo controlled, it would be beneficial if this drug is compared against systemic steroids which has been a standard of care for patient of TAO for decades. Another limiting factor for the use of Teprotumumab would be financial burden of acquiring it. Teprotumumab will cost $14,900 per vial, requiring 23 vials over a period of 6 months, and that the wholesale acquisition cost for the drug is about $343,000. The drug has also received Orphan drug designation.

Effort should be in the direction of limiting the disabilities that would develop during the active phase of the disease and closely follow up patients who might develop sight-threatening complications.

Teprotumumab is now available in India, however it is difficult to administer due to financial constraints. In our clinical practice, glucocorticoids (intravenous preferred over oral) are used in active cases of TAO and for sustained maintenance a combination glucocorticoids (oral) and cyclosporine/ azathioprine are quite effective. Rituximab is reserved for cases where Glucocorticoids are ineffective or dose limit has been reached.

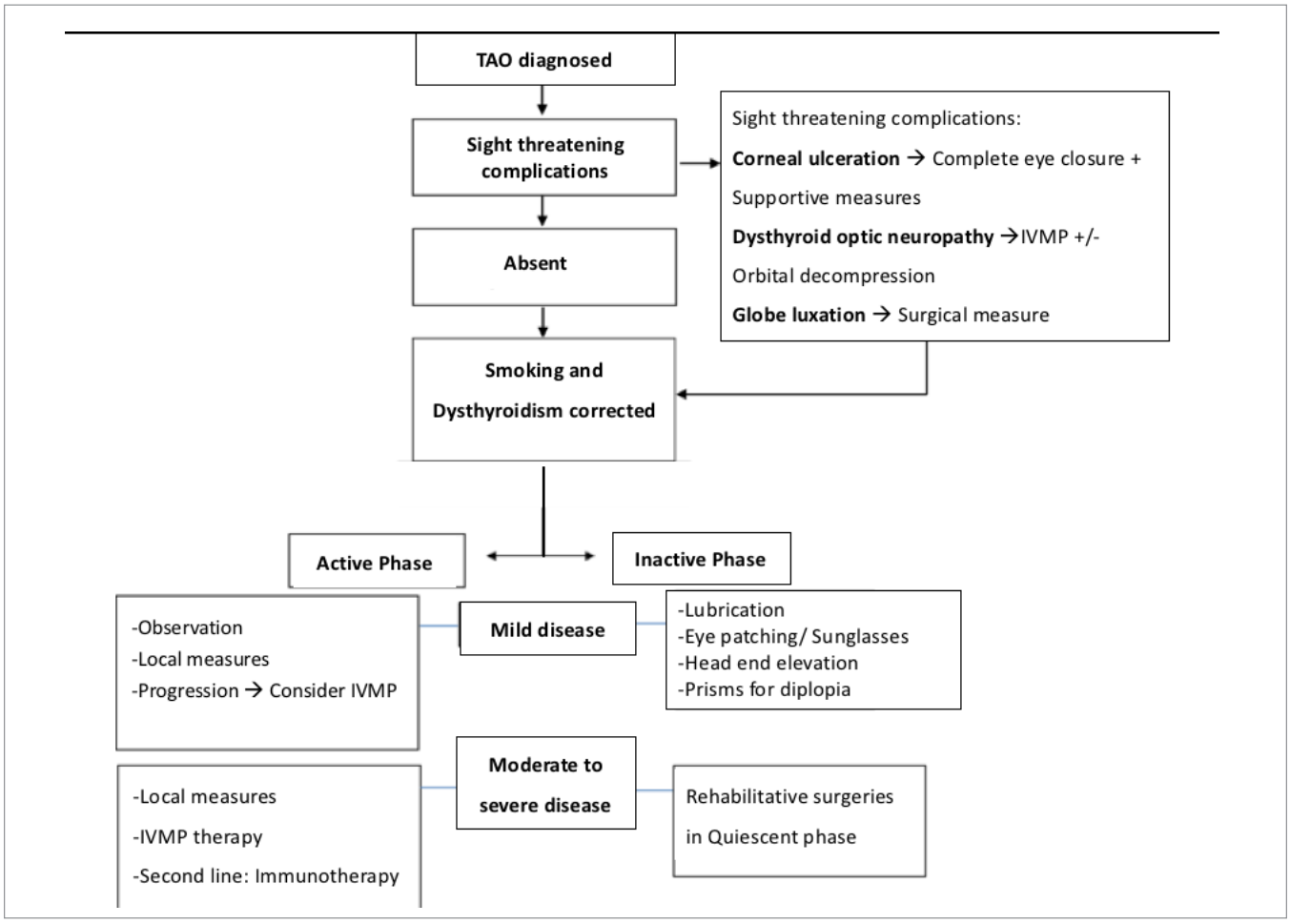


Figure 1 : *Flow Check for Management of TAQ*

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Pratibha Panmand

Photo Essay
Diagnose this

Satya Karna, Jaypee Hospital, Noida

HISTORY AND EXAMINATION

44 year old male came for detailed evaluation. He had a left upper lid retraction with treatment for thyroid since 4 years. His vision was 6/6 N6 in both eyes. Intraocular pressure was normal in both eyes. Pupillary exam did not reveal any RAPD. Ocular movements were full in both eyes and he was orthophoric. Fundus exam revealed CDR 0.7 with temporal pallor in both eyes.

The patient could not perform the automated perimetry well.

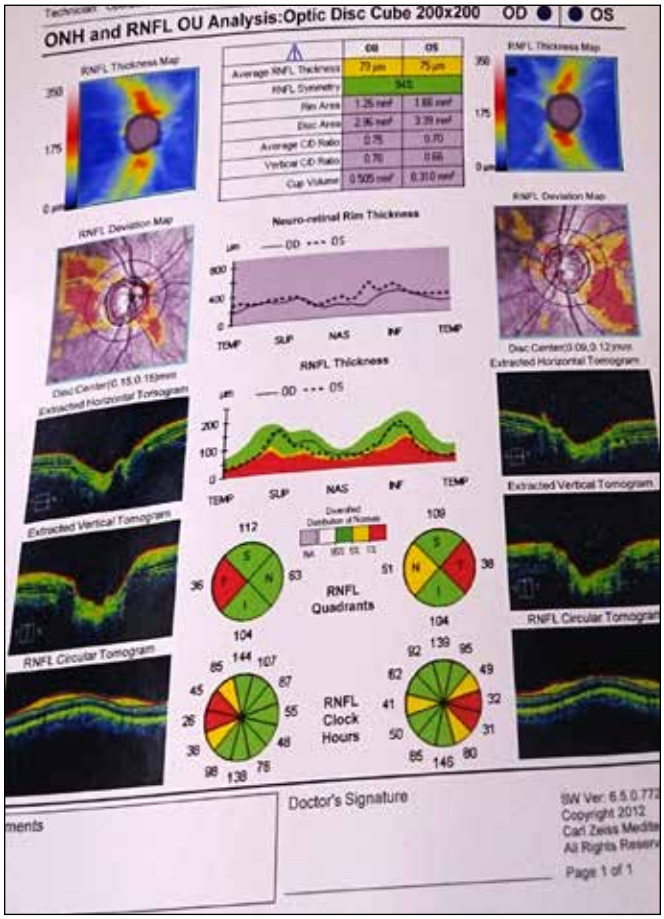

Figure 1. **OCT RNFL** showed thickness of Right eye 79 mic and Left eye 75 mic and CDR of Right eye 0.75 and Left eye 0.70.

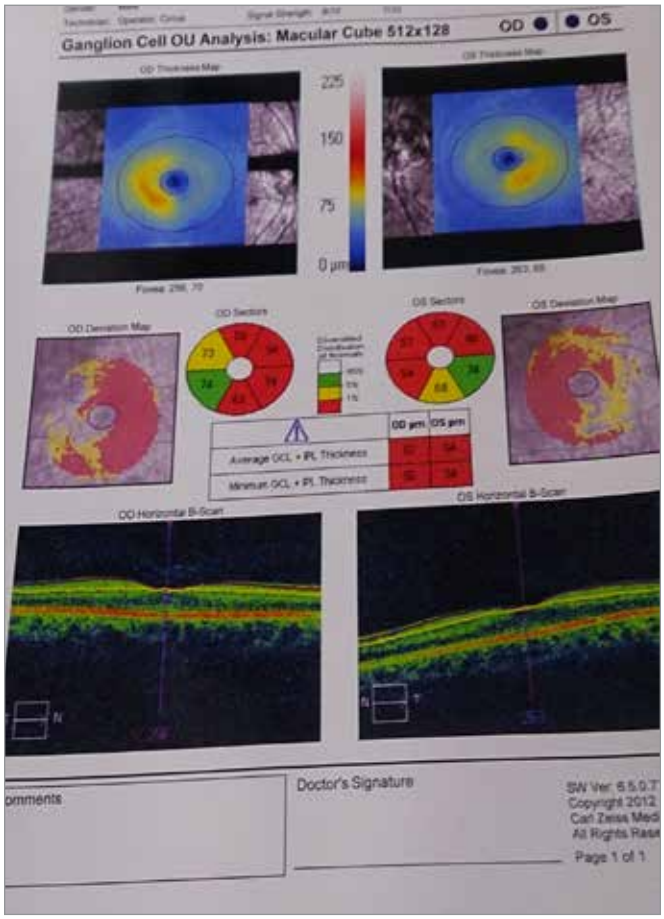

Figure 2. *GCL IPL thickness was found to be 62 mic in right eye and 64 mic in left eye.*

Where is the lesion and why? What is the likely lesion?

Satya Karna

Answers are given on page no. 23

Update

Ethambutol induced optic neuropathy: Rising Tide

Jenil Seth, LV Prasad Eye Institute, Hyderabad

Ethambutol (EMB) induced optic neuropathy is a widely recognized adverse event in patients receiving anti-tubercular therapy for mycobacterial infections. India accounts for one-fourth of tuberculosis (TB) burden and has the highest number of multi-drug resistant (MDR) cases.[1] With the increasing burden of MDR TB and related mortality, the Revised National TB control programme (RNTCP) brought changes to its treatment strategies in 2017 to a daily regimen.[2] This includes a change in dose administering strategy from intermittent to daily dose administration, fixed drug dose combinations (FDC) and definitive weight bands to administer the appropriate dose of anti-tuberculosis drugs to patients.

Ethambutol is a bacteriostatic drug given in combination with other bactericidal drugs for mycobacterial infections with a recommended safe dose of 15mg/kg body weight to minimize its adverse reactions.[3] Much has been published worldwide and in India on optic neuropathy due to ethambutol use before 2017. The incidence/ prevalence of ethambutol toxicity varies in the literature, however, the cumulative incidence reported was 19.2/1000[4] patients on ethambutol less than 27mg/kg body weight for 2-9 months with the incidence of permanent visual impairment being 2.3/1000. With the new RNTCP guidelines in 2017, ethambutol will be administered in fixed-dose combinations for new cases of TB for a period at least of 6 months irrespective of sputum negativity and positive drug sensitivity test (DST). As per the new guidelines, a patient of 65 kgs index case would receive ethambutol along with other ATT for 6 months at dose of 1110mg (275 x 4) for a period of 6 months. This leads to a daily dose of 16.92mg/kg body weight with a very high total cumulative dose of ethambutol.

Patients with ethambutol induced optic neuropathy present with gradual onset bilateral symmetrical painless vision loss in both eyes usually at an average of 2-3 months of starting ethambutol in form of FDCs (Fixed drug Dose combinations). There is an alarming rise in a number of patients with visual impairment with new drug regimen at many eye centers across India. However, there are no published reports yet with regards to the incidence of ocular adverse events as well as those of permanent visual impairment. Apart from visual loss, dyschromatopsia, decrease in contrast acuity and visual field defects are most common ocular manifestation of toxicity. Most common visual fields defects reported are central scotoma followed by bitemporal hemi field defects (Figure 1). Currently, there are no strategies adopted for early detection or identifying at-risk populations for optic neuropathy due to ethambutol use. Due to insidious onset and slow progression of vision loss, often there is delayed presentation. Earliest changes are noted on Optical Coherence Tomography (OCT) where there is the involvement of macular ganglion cell layer (M GCL) with normal retinal nerve fibre layer (Figure 2a & 2b).[6]

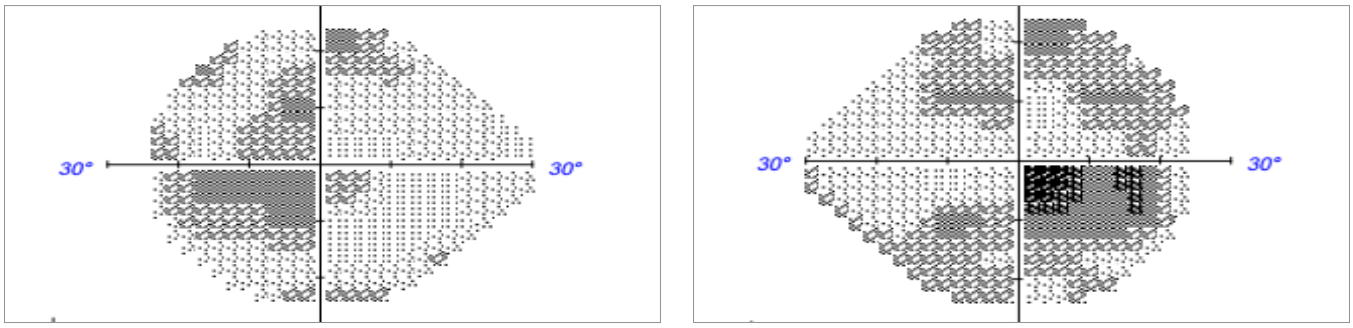

Figure 1 : *Bilateral centroceacal scotoma in a patient diagnosed of ethambutol induced optic neuropathy*

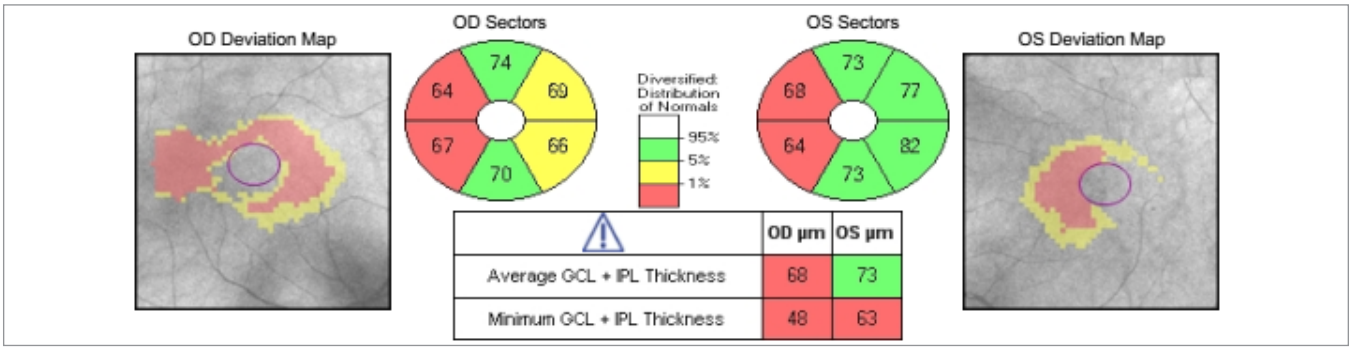

Figure 2 a : *Significant thinning of RE temporal & LE laser macular ganglion cell layer complex in either eyes in same patients suggesting of early damage*

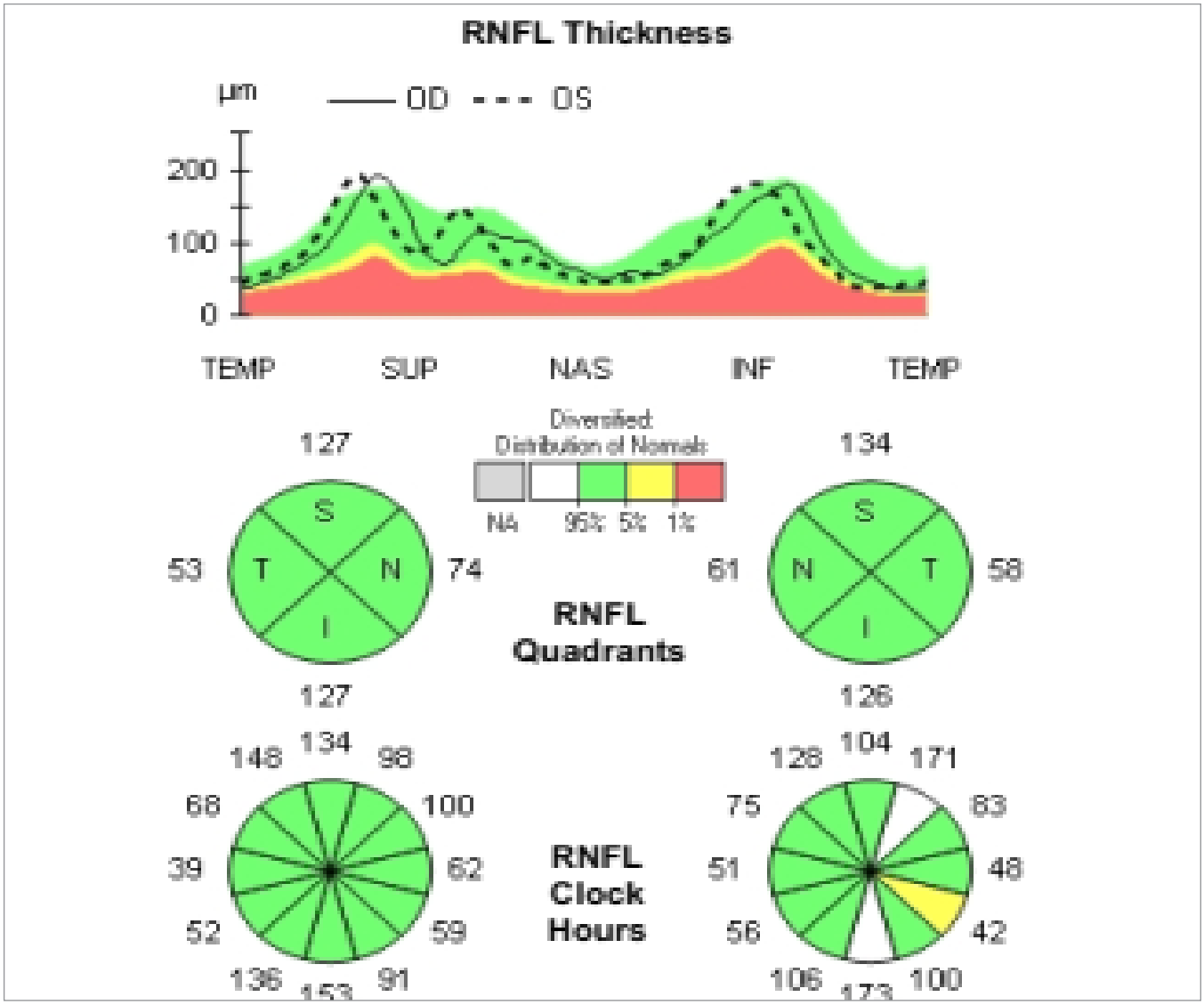

Figure 2 b : *Normal retinal nerve fibre thickness in either eyes in same patient of ethambutol optic neuropathy.*

Some studies have shown use of Visual Evoked Potentials (VEP) in early detection of toxic neuropathy with reduced P100 amplitudes with mild delayed latency. Various risk factors identified for early and aggressive toxicity are pre-existing nephropathy, diabetes, old age, known smoker or alcoholic. In an ongoing prospective study in South India across 3 tertiary eye care centers, more than 105 patients of presumed ethambutol toxicity have been recruited in 2019-20 and are been observed for various ocular parameters over period of one year. All patients included in the study had visual disturbances around 2-4 months of starting a fixed-dose combination of anti-tuberculosis treatment as per revised RNTCP guidelines. The interim analysis shows more than half the patients present with profound vision loss (worse than 20/200) at presentation, with poor visual recovery till 6 months of discontinuation of ethambutol. In the same centers, unpublished retrospective analysis of patients diagnosed of ethambutol toxicity from 2014-18, revealed an exponential increase in cases in the past 2 years.

There are no known effective treatment strategies for ethambutol induced optic neuropathy except for discontinuation of the drug. Zinc and copper supplements along with a high dose of vitamin B 12 might help with reducing oxidative stress-induced apoptosis of retinal ganglion cells. However, these are the only hypothesis and there are no prospective studies or randomized trials of its role in treatment The best strategy would be early detection and prevention of ocular adverse events. This would include

- Creating awareness of potential side effects of drug and emphasizing early reporting of side effects
- Identifying patients at risk, factoring for weight loss that would occur throughout the disease duration and tailoring the dose of ethambutol accordingly
- Basic screening of visual functions of the patient which would include – best-corrected visual acuity, color vision testing with pseudo-isochromatic charts, confrontation test
- Creating awareness amongst physician, DOTS providers about visual impairment due to ethambutol use and early reporting and referral to appropriate health care provider
- Regular monitoring of patients at risk – like those with an abnormal color vision to begin with, old age, cases of recurrent TB, HIV positive patients, renal function impairment
- To discuss with policy makers and health planners about increasing incidence of ethambutol induced visual impairment, reducing duration of ethambutol intake in sputum negative or DST negative cases, implementation of basic vision screening tests at DOTS center before starting anti-tuberculosis drugs. It would be appropriate to start a National Registry of Ethambutol Optic Neuropathy with an endeavor to have accurate reporting of cases and outcomes.

Jenil Seth

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Review

Understanding Ganglion Cell Layer and Inner Plexiform Layer: an Indispensable Companion in Neuro-Ophthalmology Clinic

Mohan Kannam, Ramesh Kekunnaya, Virender Sachdeva, L V Prasad Eye Institute, Visakhapatnam & Hyderabad

INTRODUCTION:

Optical coherence tomography (OCT) is one of the most common imaging modalities available in our neuro-ophthalmology clinics. In glaucoma and neuro-ophthalmology practice, advent of OCT has made possible to assess the retinal nerve fiber layer (RNFL) defects and neuro-retinal rim changes observed quantitatively by assessing the same. In addition, the observation of the detailed scans gives information similar to histological sections, so that various pathologies can be well characterized. In addition, other advantages such as non-invasiveness, accuracy, and reproducibility, make OCT an indispensable tool in evaluation of patients with diseases of the afferent visual pathways.

In the last decade with advent of spectral domain OCT (SD-OCT) imaging of macular ganglion cell-inner plexiform layer (mGCIPL) complex became possible. This has facilitated greater understanding of many conditions by enabling us to detect the damage to optic nerve early and monitoring during the follow-up early. This article focuses on interpretation and importance of MGCIPL analysis in the neuro-ophthalmic conditions.

What is macular ganglion cell inner plexiform layer (mGCIPL) analysis and why is it important?

Macular ganglion cell layer -inner plexiform analysis refers to the analysis of the following layers at the retina: ganglion cells, inner plexiform layer and internal limiting membrane, however, the maximum information signal comes from the retinal ganglion cell layer thickness. The macular ganglion cell layer (mGCIPL) gives analysis of the retinal ganglion cells in the perifoveal area that ultimately form the axons passing though the optic nerve. Therefore, in diseases affecting the afferent visual pathways, mGCIPL analysis reflects damage to the cell bodies of axons in the anterior visual pathways.[1] Further, mGCIPL analysis can detect changes in many neuro-ophthalmic conditions earlier than the RNFL analysis, as cell death/apoptosis starts in cell body of neurons much before the loss of axons which shows up in RNFL analysis. Thus, mGCIPL not only provides a surrogate measure of pRNFL thickness but additionally might show changes earlier than pRNFL analysis.

Further, it provides a good estimate of the remaining cells in the perimacular area, which might help us predict the recovery in various neuro-ophthalmological conditions. e.g. disc edema, compressive optic neuropathy, toxic optic neuropathy, and demyelinating conditions like multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD) and anti-myelin oligodendrocyte glycoprotein (MOG) antibody optic neuritis.

How is mGCIPL analysis performed in various machines?

As mentioned above, mGCIPL analysis measures area pertaining to retinal ganglion cells, inner plexiform layer and internal limiting membrane.(Figure 1)

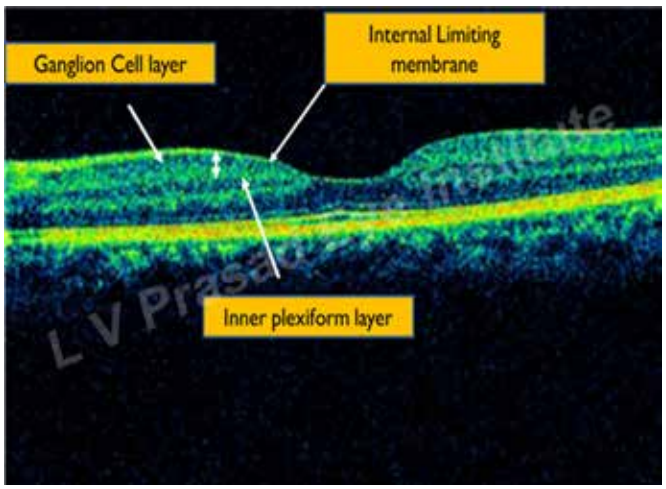


Figure 1 : *Showing the layers of retina that comprise the ganglion cell layer-inner plexiform layer analysis.*

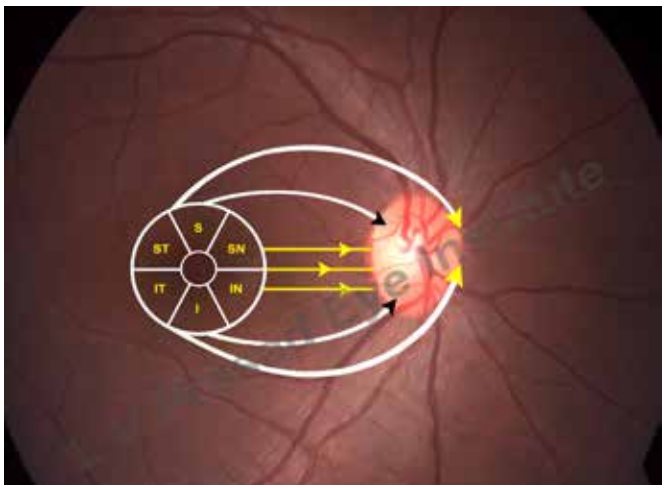


Figure 2 : *Showing the distribution of the perifoveal area into six different zones. The fibers from the perifoveal ganglion cells in each zone project to the optic disc in different areas.*

However, this protocol was not available in the time domain OCT (TD-OCT), but became possible with the newer spectral domain OCT (SD-OCT). Different machines use different patterns of segmentation and give slightly different values of the thickness. In a landmark paper, Meshi et al have compared the differences in the ganglion cell analysis provided by different machines.[2] The most commonly used machines are the Cirrus HD-OCT (by Carl ZessMeditec, Inc., Dublin CA, United States),[3,4] RTVue (Optovue, Inc., Fremont, CA, United States), 5Spectralis(Heidelberg Engineering, Heidelberg, Germany)[6] and 3D OCT 2000 (Topcon Corporation, Tokyo, Japan).[7] Although all of them measure the GCIPL thickness however, they differ slightly from each other in the actual thickness measures, width of the scans, sensitivity of the machine, representation of the average and region wise thickness. Interested readers can refer to the article by Meshi et al[2] and the manuals of each machine.[3-7]

What is the topographic arrangement of nerve fibers at macula contributing to mGCIPL?

GCIPL is divided into 6 segments, namely, superior (S), Supero-temporal (ST), Supero-nasal(SN), Inferior(I), Infero-nasal(IN) and Infero-temporal (IT). These six areas are so chosen as they represent the fibers arising from different parts of the perifoveal RGCs.

Fibers from the SN and IN area run in the temporal raphe and enter the optic disc in the temporal portion; superior and inferior quadrants represent the superior and inferior arcuate fibers and fibers from the ST and IT quadrant represent the superior and inferior radiating fibers that enter the disc on the nasal aspect. This is important to remember as it gives an idea about the patterns observed in pathologies affecting focal areas. (figure 2)

How to read a macular OCT report-A Step wise approach (Figure 3)

1. Cross check patient details; name, age, gender,and good signal strength (≥ 8, at least 6)
2. Look for proper centration (circles in the thickness maps are well centered over the macula)
3. Rule out any motion/blink artefacts (black areas) or segmentation errors.
4. Look at horizontal B-scan of the macular scan that suggests possible co-existing macular pathology and segmentation analysis that might give error in measurement of the GCIPL software (figure 4).

5. Examine deviation map for color coding; red (thinned out), yellow(borderline) and none (normal)

6. Look at the average/ minimum thickness and its color coding (red, yellow, and green) indicating probability of thinning compared to age matched individuals (this gives a comparison of the values of patients when compared with the age and gender based normative database).

7. Sector-wise distribution of the GCIPL thickness, it gives values in the six segments which gives an estimate of the area of the retina that are affected.

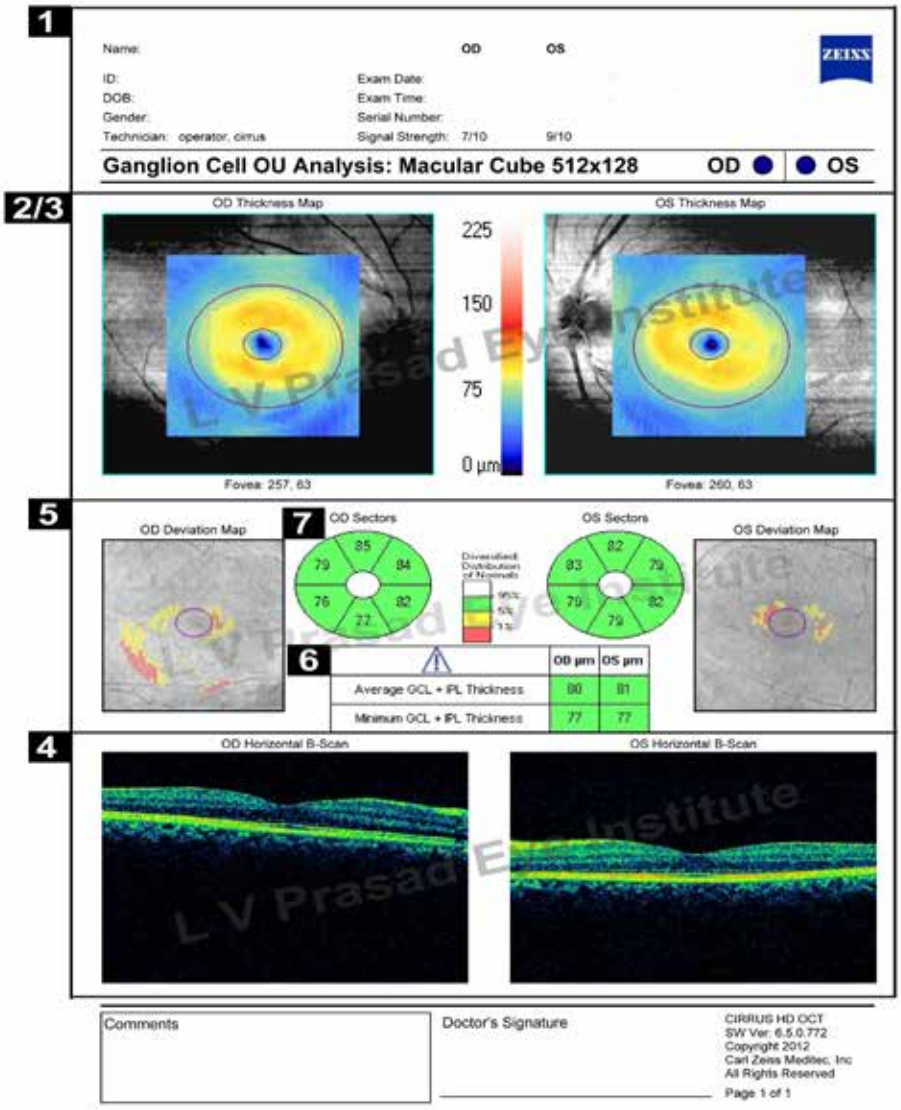


Figure 3 :

Notes: 1) Sometimes in patients with severe disc edema especially with associated significant peripapillary/ macular edema, segmentation errors might occur and there might be errors in the MGCIPL analysis.

2) As mentioned in the point 5, one should look for co-existing macular scarring, epiretinal membrane or edema that might make our observations inaccurate and prevent us from making accurate judgements. An example is shown below in Figure 4 which shows the false low mGCIPL thickness in a patient with co-existent subretinal fluid at macula.

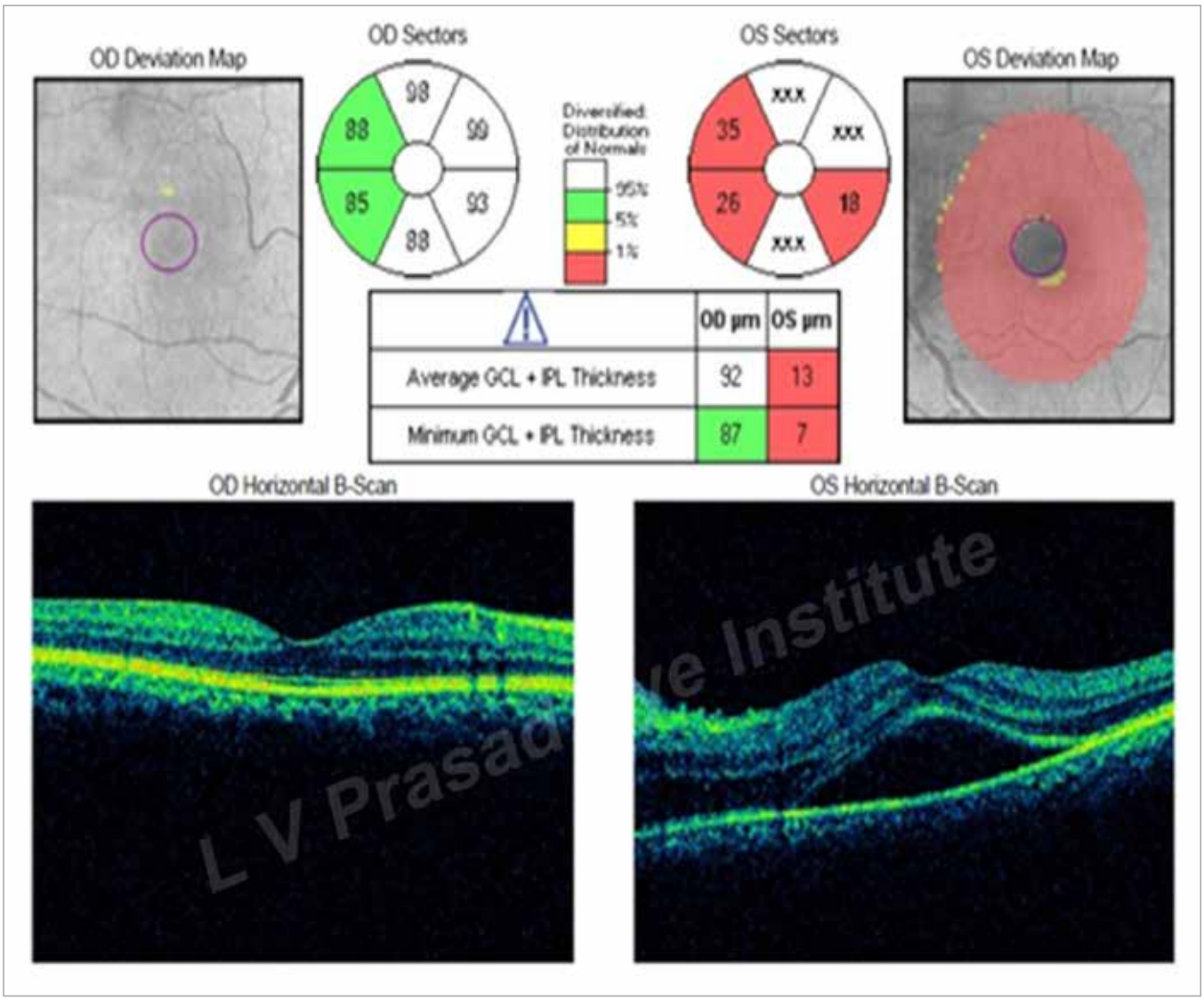


Figure 4 : *Demonstrating error in measurement in GCL analysis due to co-existing macular pathology (subretinal fluid) in this patient. This led to errors in segmentation leading to unexpectedly low MGCIP thickness.*

Application advantage of mGCIPL in the neuroophthalmology clinics

1.GCIPL more rapid detection of structural damage:

(Figure 5) As briefly mentioned above, MGCIPL analysis can show damage in the macular ganglion cell layer earlier than RNFL. e.g. in patients with optic neuritis, multiple studies [8,9] reported that patients with optic neuritis had visible mGCIPL thinning at 4 weeks itself while pRNFL was normal or showed minimal thinning. In addition, GCIPL showed greater correlation with VA and VF than RNFL in optic neuritis patients on 6 months follow up.[9]

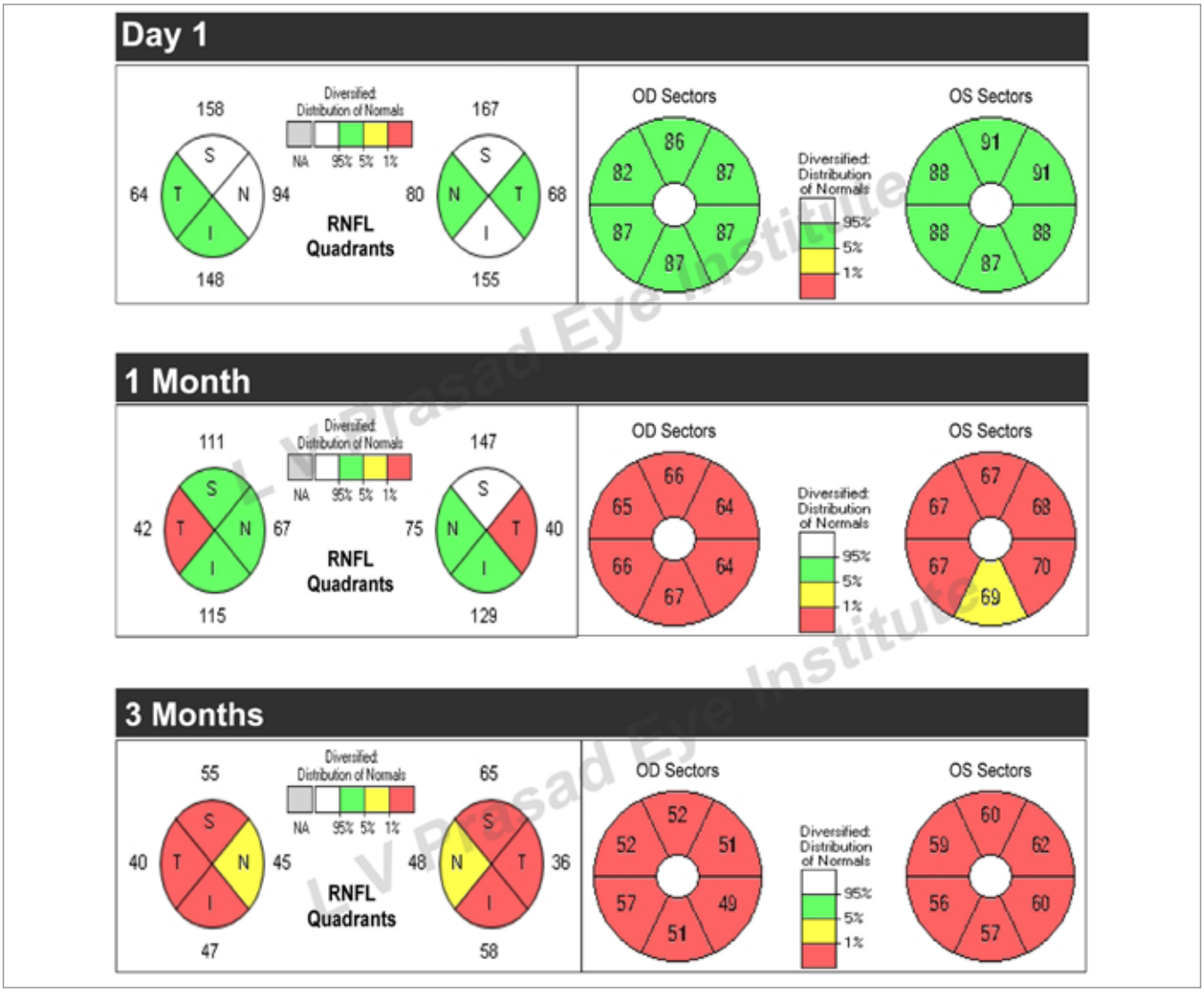


Figure 5 : *Shows representative photograph of a patient with acute optic neuritis showing mild increase in RNFL thickness in BE at presentation but normal ganglion cell thickness (top-panel). At 1-month follow-up we can observe mild RNFL thinning but significant thinning of mGCIPL layers (middle panel). The last panel shows that at 3-month FU significant thinning is observed in both RNFL and GCIPL in both eyes. This composite picture shows ganglion cell layer analysis is more sensitive to detect structural damage than RNFL analysis on OCT.*

Similarly, Akbari et al, in their study published GCIPL thinning is first detectable at 1 month after NAAION and persists for 3 months and GCIPL thinning occurs even before RFNL thinning is detectable in NAION patients.[10]

2.GCIPL role in disc edema:

Peripapillary RNFL thickness OCT scan can underestimate RNFL damage in setting of disc edema (optic neuritis/papilledema).GCIPL thickness can give us early structural changes in these cases especially in the early phases. This is because, there is no nerve swelling per se at macula and early structural changes appear in the perimacular ganglion cells while pRNFL might remain stable or reduce only slightly.[8,9] (Figure 6)

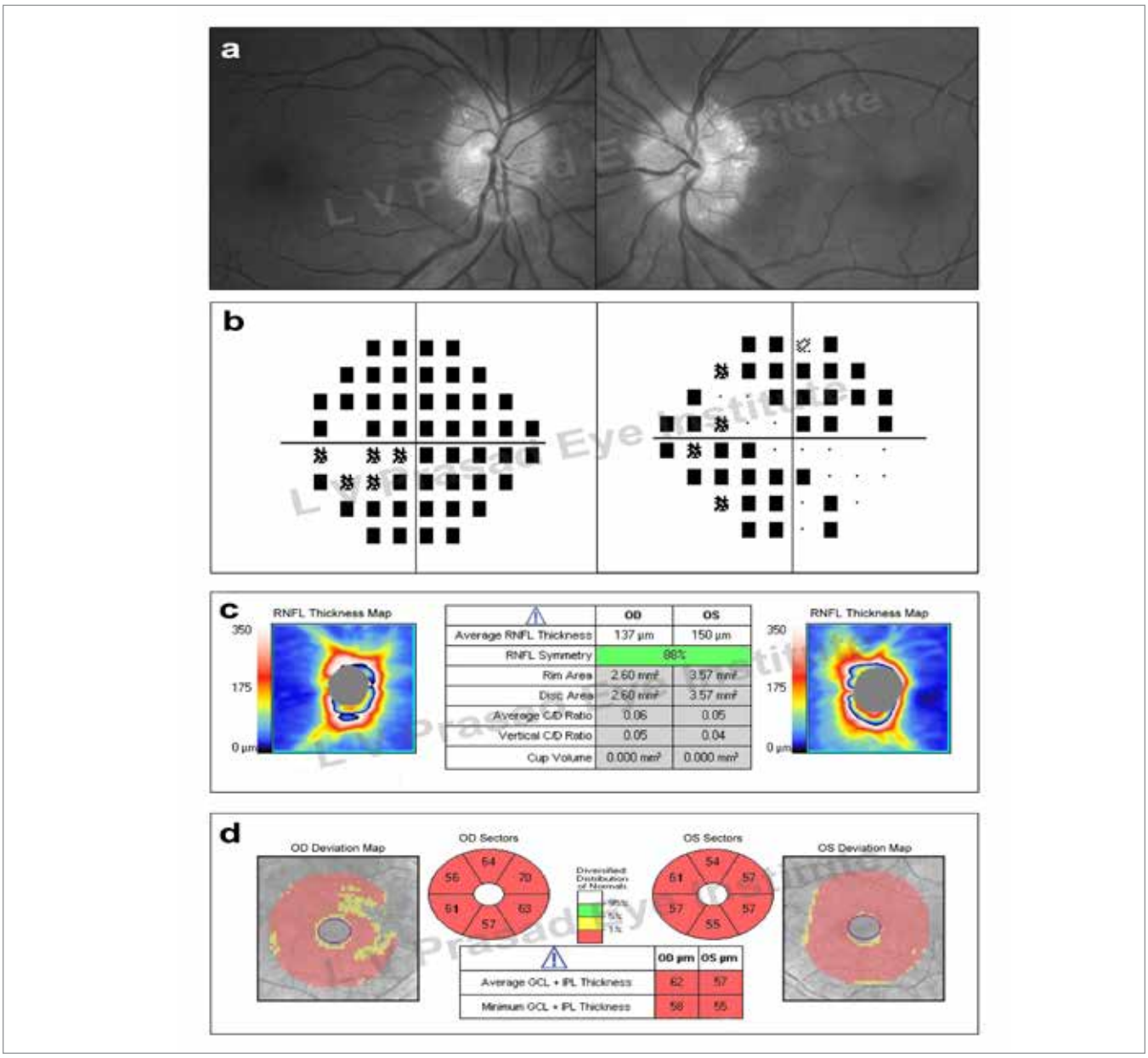


Figure 6 : *Shows representative photograph of a patient with chronic disc edema. We can observe chronic disc edema in BE (top panel), advanced field defect in the left eye and reduced GCIPL thickness in BE. Thus, showing importance of GCIPL layer thickness in early structural damage in a case with disc edema where RNFL thickness can be erroneous.*

As a corollary it might also be interpreted, in a patient with disc edema, reduction of RNFL thickness but associated mGCIPL thinning indicates permanent RNFL damage might be settling in. This might be accompanied by worsening of the visual fields as well.

3. GCIPL role in structure -function correlation

As we observed before, there is a topographic distribution of the retinal fibers in the mGCIPL.It is likely that patients with focal damage to the anterior visual pathways such NAION, compression from pituitary lesions, can give corresponding structure - function correlation (figure 7). Studies have shown that GCIPL thickness had stronger correlation with visual field than RNFL thickess.[10,11]

E.g.mGCIPL thinning is seen at corresponding sectors of the sector-wise map in a patient with NAAION corresponding with inferior arcuate/ altitudinal defect.

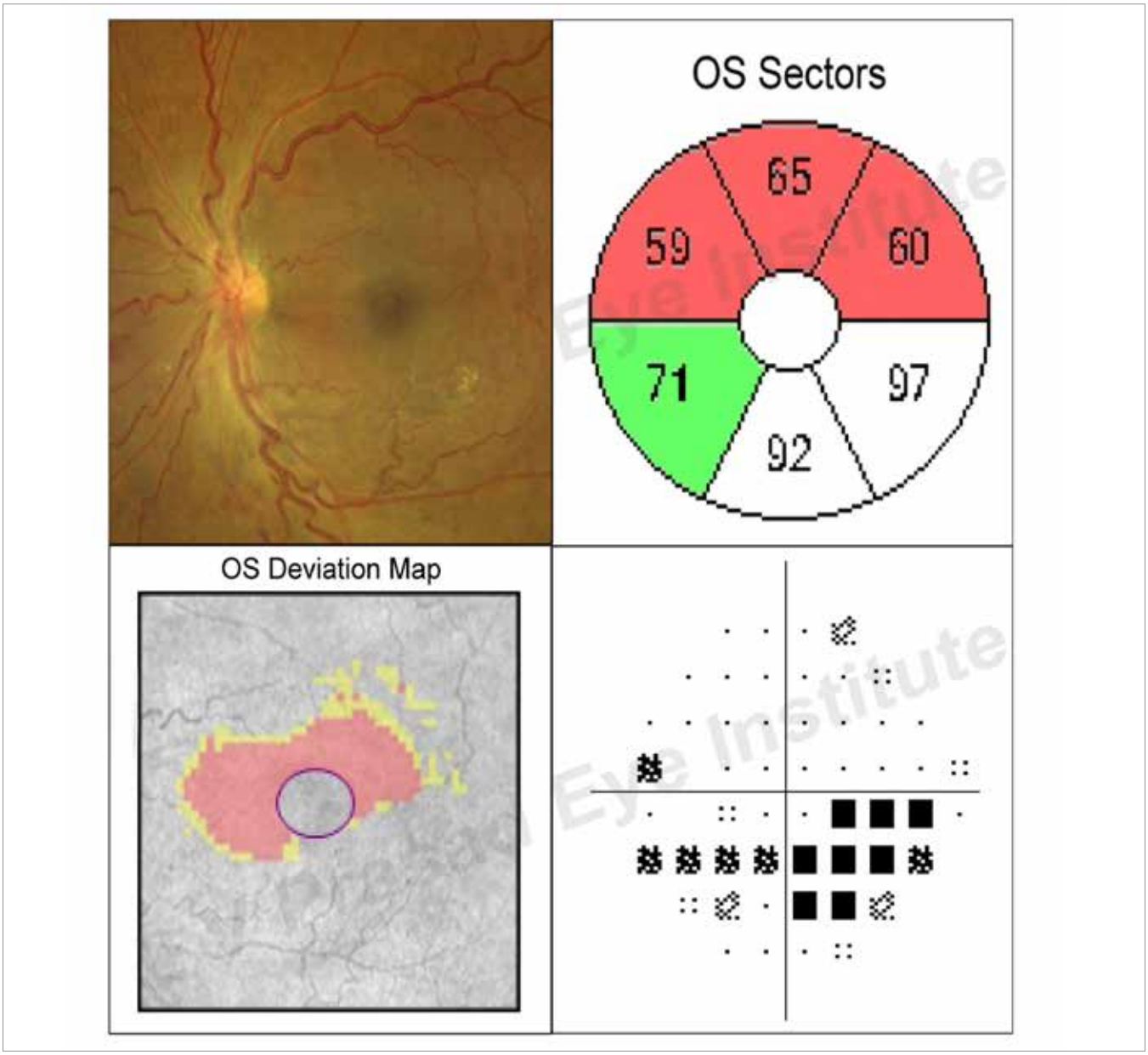
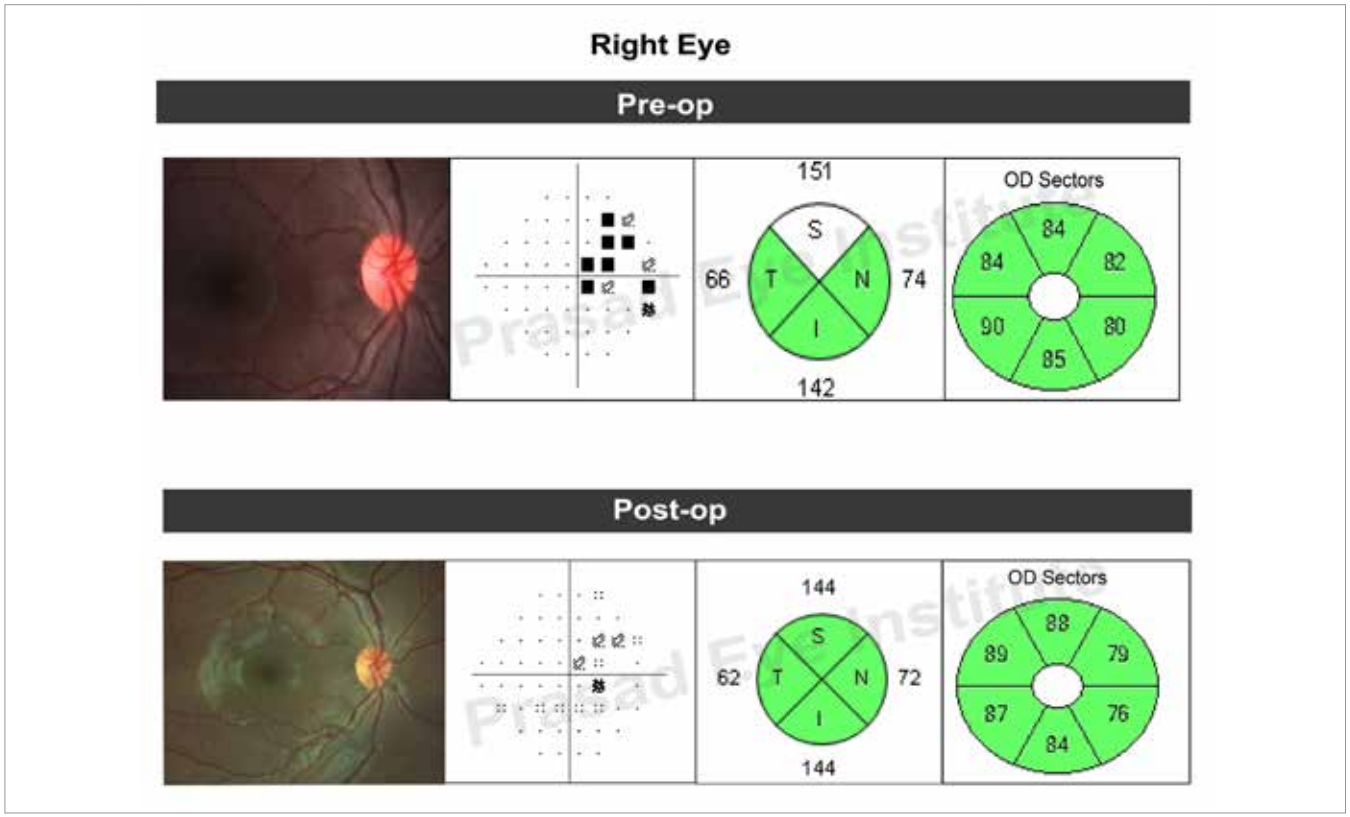


Figure 7 : *Composite photograph showing a patient with superior half disc pallor(top left), superior thinning on the sector wise distribution plot and deviation map (top right and bottom left) and corresponding inferior arcuate field defect (bottom right) in a patient with Non-arteritic anterior ischemic optic neuropathy (NAAION).*

4.GCIPL in predicting visual recovery and following patients in compressive optic neuropathy

In a patient with compressive lesions of the anterior visual pathways, OCT parameters might help us in judging the structural loss and estimate residual nerve fiber available. This might give us clues to the final visual outcomes. This can be done using the RNFL and mGCIPL OCT, however, as mGCIPL is more sensitive to structural damage.[12]

Laowanapiban et al reported that in patients with pituitary tumors, early thinning is localised to nasal hemiretina on mGCIPL and corresponding temporal RNFL of the optic nerve head and mGCIPL analysis was more consistent.[13] These patients might show greater recovery as compared to patients with advanced damage with diffuse RNFL and mGCIPL thinning.



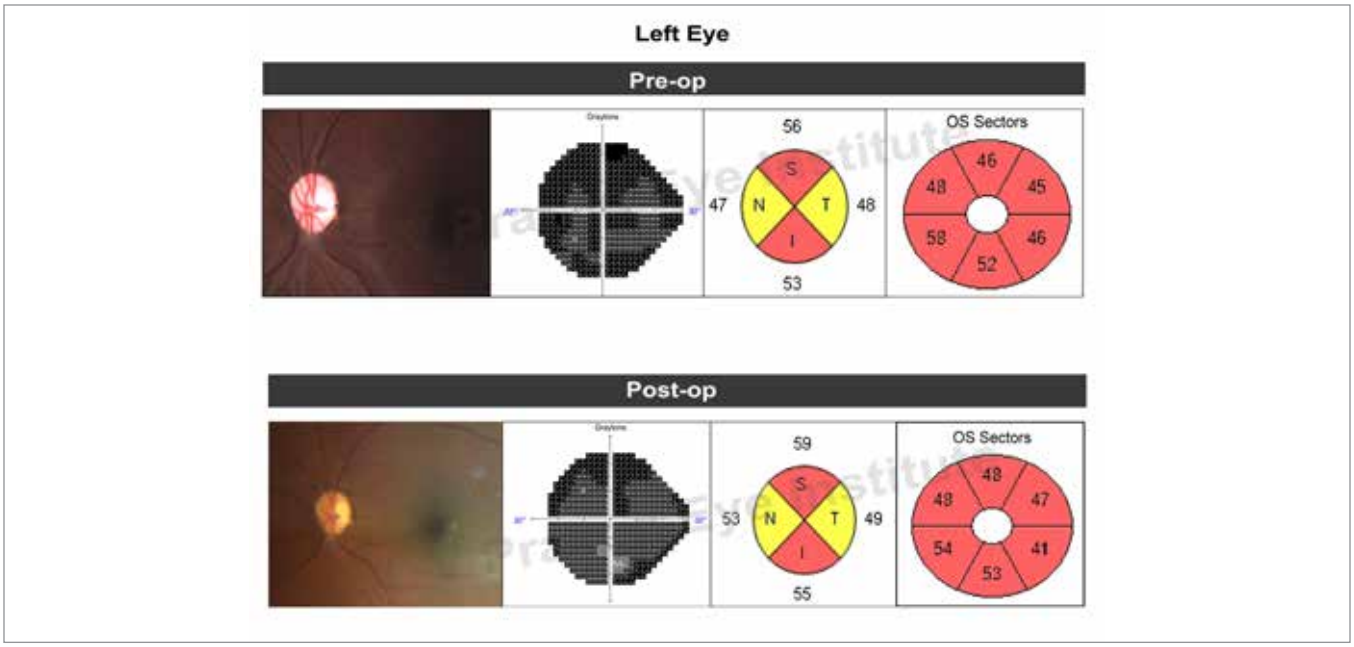


Figure 8 & 9 : *Composite photograph of a patient with pituitary tumor, visual field changes and OCT parameters pre and 3 month post-operatively in right and left eye of the same patient.*
Right eye : *showing mild optic disc pallor, early temporal hemianopic field defect in right eye and early nasal crescentic field defect with good recovery.*
Left eye : *showing diffuse optic disc pallor, advance field loss (possibly using only the stimulus V target), diffuse RNFL and MGCIPL thinning with poor improvement in visual field post-operatively*

Another important use of mGICPL analysis could be following patients with compressive anterior visual pathway lesions such as pituitary tumors compressing the optic chiasm and chiasmal gliomas. In children with chiasmal gliomas it may not be possible to achieve formal visual fields. Therefore, OCT plays a major role in monitoring structural damage. mGCIPL analysis again is more sensitive than RNFL analysis in monitoring structural damage in these patients.[14]

Caution: We must remember that in both these roles OCT may not accurately correlate with visual recovery or always precede the damage in visual fields as there could be neuropraxia due to compression of the fibres in the visual pathways, and also redundancy of the fibres.[15] So, recovery might occur despite OCT showing significant thinning as the compression is relieved and surviving cells start functioning again. Similarly, worsening of the visual function might be evident on visual fields secondary to axonal compression might also occur before actual loss of axons is detected by the OCT.

Therefore, visual fields and OCT should both complement each other.

5.GCIPL in toxic / nutritional optic neuropathy:

Patient with acute toxic optic neuropathy might have severe vision loss and markedly depressed visual fields. In these patients, OCT assessment of the structural damage at 3-4 weeks might again correlate with the final visual outcome.

Lee et al, found that GCIPL is the early structural marker reflecting axonal damage in ethambutol toxicity.[16] Theyfound average mGCIPL thickness and mGCIPL thickness in the nasal quadrants negatively correlated with the degree of vision recovery.[12] Similarly,In conditions like methanol poisoning that present with disc edema in acute stages RNFL thickness might again be increased, thus mGCIPL might be more reliable indicator.

6. GCIPL in follow up of multiple Sclerosis/ demyelinating diseases:

As we know lifelong follow up by neurologist is mandatory in patients with multiple sclerosis (MS). They can have either recurrent clinical/subclinical optic neuritis causing thinning of pRNFL and mGCIPL thickness. Subclinical episodes might be missed by patients/treating neurologists in follow up in the setting of near normal visual acuity.

Macular GCIPL is more sensitive and shows thinning in these episodes even in subclinical episodes even before pRNFL thinning is shown.[17] Secondary progressive MS (SPMS) type shows more advanced thinning of mGCIPL than other MS types.[17] Walter et al demonstrated that mGCIPL thinning is significantly correlated with visual function in MS patients with and without a history of acute ON and may serve as a useful structural marker of the disease.[18]

Another important observation is that patients with MS vs. other demyelinating diseases such as NMO and MOG, tend to have different amount of RNFL and MGCIPL loss even after the first episode of optic neuritis. Patients with NMO and MOG optic neuritis tend to have greater RNFL and MGC-IPL loss as compared to MS or post-infectious optic neuritis.[8] This might have implication in both prognosticating, deciding the further course of treatment and formulating a differential diagnosis.

7.GCIPL role in follow up of degenerative conditions (Alzheimer's disease)

Alzheimer's disease (AD) is the most common age-related dementia and is characterized by the accumulation of amyloid-β protein (Aβ) plaques as well as aggregates of hyperphosphorylated tau as neurofibrillary tangles in the brain.Choi et al, reported that mGCIPL is useful biomarker for monitoring disease progression than pRNFL.[19] Gomerio et al have suggested that there might role of perfusion differences in macular area as compared to the rest of retina. RGCs in macula have highest activity which implies possibility of neuronal hyperexcitation. Further, as fovea does not contain blood vessels, reduced supply of

oxygen and nutrients leads to tissue hypoxia in AD.20 Therefore, MGCL analysis might play a role in early detection of the structural damage in AD.

In conclusion, mGCIPL analysis is an important tool in analysis of patient with various neuro-ophthalmological conditions. It gives not only supplementary information to the RNFL analysis protocol but also has distinct advantages of being able to detect structural damage early and even in setting of disc edema. This might give us early clues to possible treatment options and assessing visual recovery in these patients.

Mohan Kannam

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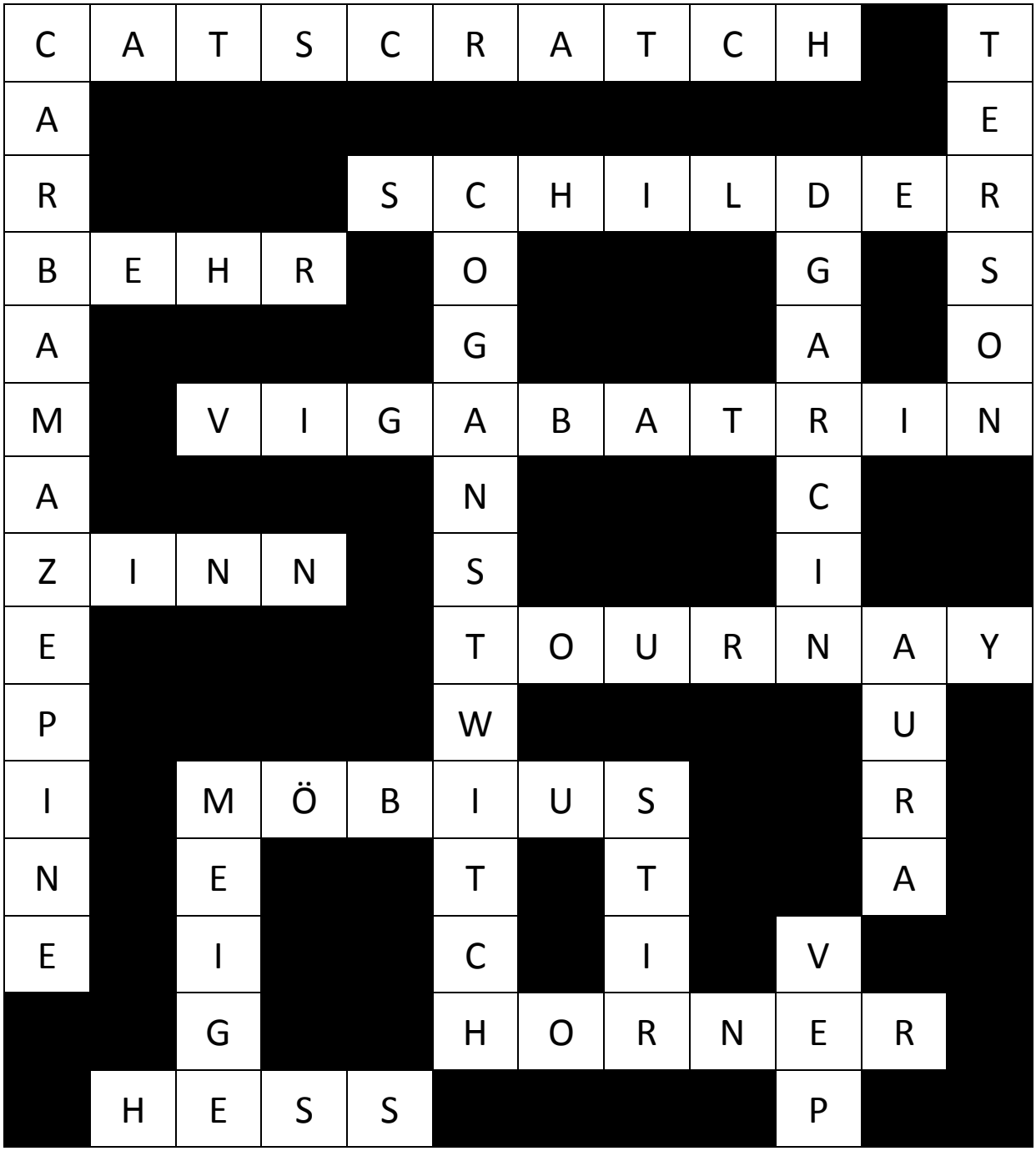
Crossword Answers

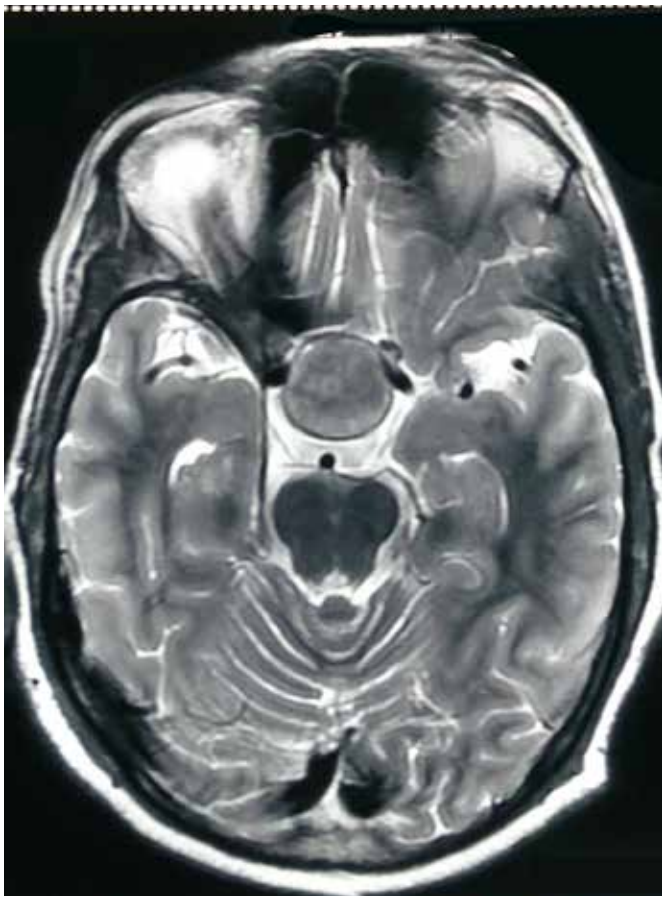


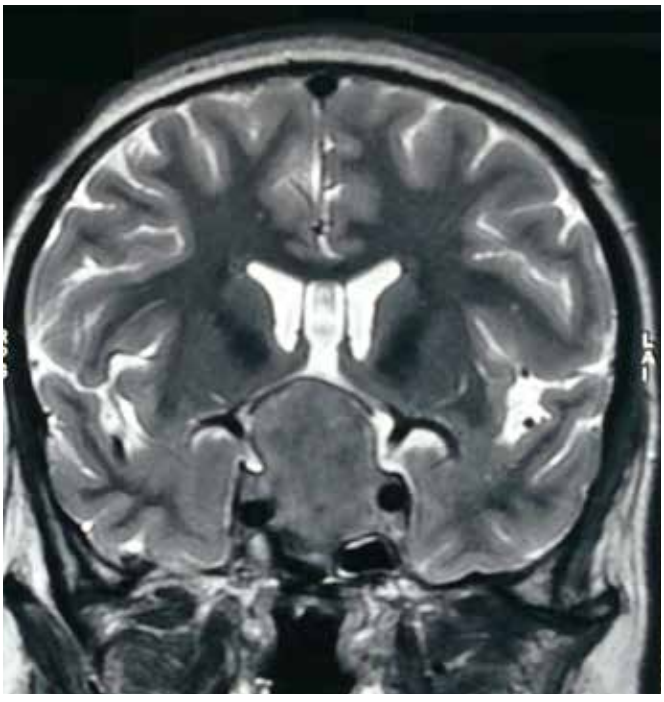
Answers for Diagnose This

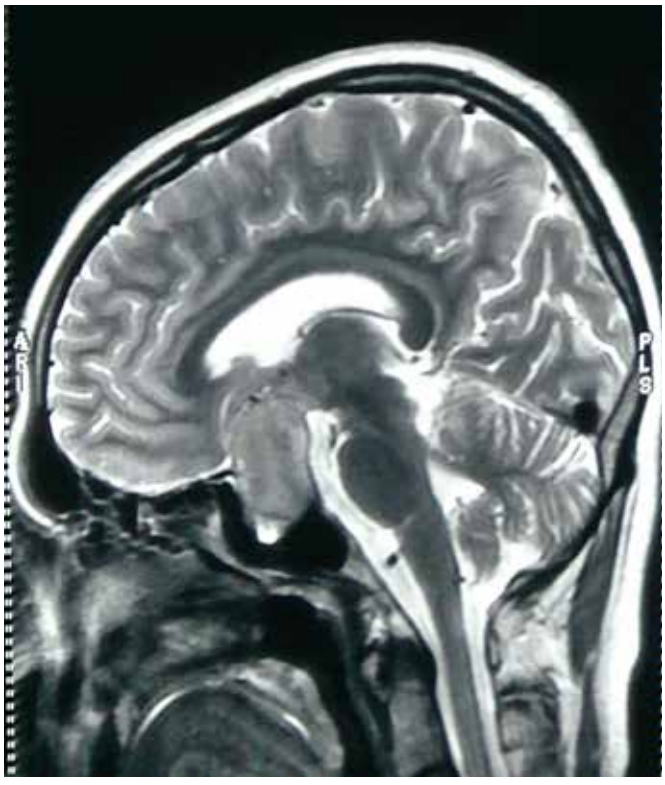
ANSWER:

The patient had asymmetric temporal to nasal thinning of RNFL in both eyes with the sectoral **RNFL** thickness in Right eye Temp 36 mic, Nasal 63 mic and in Left eye Temp 38 mic, Nasal 51 mic, similar to early compression of visual pathway in midline compressive lesions. More significantly, bilateral thinning of **GCL-IPL**, more in the **nasal halves**, with respect to the fovea/fixation (in the Ganglion cell analysis Deviation maps) are suggestive of visual field defects of **bitemporal hemianopia**. The lesion is localized in the Optic chiasm, therefore there is no RAPD in either eye.

The Axial, Coronal and Sagittal T2W MRI (Fig. 3 a,b,c) shows figure of eight shaped pituitary adenoma compressing and splaying the optic chiasm upwards. In chiasmal compression, OCT RNFL and GCL-IPL changes may appear along with visual field defects. Hence, OCT is an essential tool in Neuro-ophthalmology.







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