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Original Research Article

ANALYSIS OF ETHAMBUTOL OCULAR TOXICITY BY SD-OCT

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Abstract:

Aim: Assessment of ethambutol optic neuropathy by nerve fibre layer and ganglion cell layer analysis using OCT

Materials and methods: It was an observational, cross sectional study. Twenty-five patients with history of taking ATT were studied in 1yr duration (Sept 2019-Aug 2020). All patients underwent a neuro-ophthalmic examination including visual acuity, colour vision, visual fields and fundus.OCT was performed on both eyes of each patient using nerve fibre layer and macular analysis protocol. Similar age match control group were taken.

Results: Male patients showed dominance (68%).Reduced VA and colour vision defect was observed. Average RNFL thickness in EON patients were 66.00±10.24µm, 94.23±12.23 µm in healthy controls ($p<0.0001$).In EON patient severe thinning observed in temporal quadrant RNFL thickness ($p<0.01$).Average GCL±IPL thickness were 64.12±10.22 µm in EON, 83.30±8.32 µm in control group ($p<0.0002$).

Conclusion: A decrease in RNFL thickness was observed in all quadrants in patients with ethambutol induced optic neuropathy, but more pronounced in temporal quadrant. Hence careful use of ethambutol must be analysed.

Keywords- EON, OCT, RNFL,GCL

NO FINANCIAL INTEREST

1. INTRODUCTION

Ethambutol (EMB), the first-line drug used to treat mycobacterium tuberculosis, is a common cause of toxic optic neuropathy. EMB-induced optic neuropathy (EON) has been reported in 1% to 5% of all patients, accounting for 100,000 new cases per year **[1–3].** The exact mechanism of Ethambutol ocular toxicity remains to be established; however, it has been known that it might result from decreased levels of copper in mitochondria or from accumulation of zinc in lysosomes of retinal ganglion cells **[4, 5].**EON is characterized by dyschromatopsia and gradual visual loss of bilateral eyes. Since a delayed diagnosis of EON carries the risk of irreversible visual loss, early detection of EON and early stoppage of EMB are required **[6].**Unfortunately, there are no obvious predisposing or risk factors to contribute to the poor visual gain after stoppage of EMB **[7–9]** The degree of reversibility accords with the time of detection; in fact, early detection and immediate termination of therapy are the only effective means of preventing progression and facilitating recovery **[10, 11].**

Optical coherence tomography (OCT) is a non-invasive imaging tool that is widely available in many eye centers. It provides quantitative and qualitative information on the anterior and posterior segments of the eye. The measurement of RNFL can be an objective

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measurement of nerve swelling or nerve atrophy by analyzing the ganglion cell complex, OCT can help to detect early axonal damage and may predict the visual outcome**[12].**

2. MATERIAL AND METHOD

The study was observational, cross-sectional study carried out in the Department of Ophthalmology, tertiary health care centre during the period of September 2019 to August 2020.A total of fifty eyes of 25 subjects with history of taking ATT were studied in 1yr duration and healthy controls of similar age matched group were taken.

Inclusion criteria

- All Patients who were on ATT or completed ATT for pulmonary and extra-pulmonary causes.
- Slowly progressive visual loss accompanied by dyschromatopsia after taking EMB.
- Age group 18-65 years.
- Those who were willing to participate in the study.

Exclusion criteria

- Patient with any media opacity, Age <18 years,>65years
- The presence of concurrent retinal diseases, any history of glaucoma, Myopia, Retinitis pigmentosa, macular pathology and ocular surgery except for cataract surgery.

MEDICAL HISTORY AND PERSONAL HISTORY

History of any systemic disease like diabetes, hypertension, hypercholesterolemia, tuberculosis. Neurological symptoms like weakness or difficulty in moving limbs, history of any nutritional disease ,history of smoking or tobacco addiction or alcohol intake.

HISTORY OF OPHTHALMIC COMPLAINTS

All study participants underwent a detailed ophthalmologic examination, including assessment of refraction, best-corrected visual acuity (BCVA), color vision, relative afferent pupillary defect, slit-lamp examination, tonometry, and a fundus examination. Data on sex, age, duration of taking EMB, BCVA at first visit.

GENERAL EXAMINATION

General condition of patient assessed as poor/moderate/fair. Pulse rate, pallor, icterus, clubbing, lymphadenopathy, neurological deficit evaluation was done. Blood pressure was recorded.

SYSTEMIC EXAMINATION

Systemic examination was done properly especially central nervous system, to detect any gait abnormalities, ataxia, weakness or numbness.

OPHTHALMIC EVALUATION-A comprehensive ophthalmic evaluation was done as

1) Visual acuity
2) Ocular movements
3) Pupillary assessment
4) Slit lamp examination of the anterior segment, lens and vitreous
5) Fundus evaluation by indirect and direct ophthalmoscopy

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6) Spectral domain optical coherence tomography (Zeiss Cirrus 500 OCT, Carl Zeiss

1).VISUAL ACUITY (VA)

Visual acuity (BCVA) was recorded by Snellen's chart at 6 meter distance at presentation then converted into Log MAR units for evaluation. On the basis of visual acuity of patient at presentation, they categorised as visual acuity less than 3/60 of Snellen's chart referred as blindness, VA <6/60 as severe vision loss (SVL),VA < 6/18 as moderate vision loss (MVL), VA<6/12 as mild vision loss and VA>6/12 considered as normal.

2) OCULAR MOVEMENTS

Ocular movements were checked in all diagnostic position gazes of direction. Associated pain with ocular movements was noted.

3)PUPILLARY ASSESSMENT-Torch light examination in individual eyes done for RAPD evaluation by swinging flash light for 3 seconds pause in each eye in a darkroom and grading done as 1,2,3,4 and 5 similar as Bell RA et al described in their study.

4) SLIT LAMP EXAMINATION-Evaluation of anterior segment done by slit lamp bio microscope to notify further findings.

5) DILATED OPHTHALMOSCOPY: DIRECT & INDIRECT-The pupils of all subjects were dilated using a combination of 0.75% tropicamide and 2.5% phenylephrine eye drops. Tropicamide 1% was used in hypertensive patient. Slit lamp indirect ophthalmoscopy with volk +90D lens and indirect ophthalmoscope was used to evaluate disc findings, under headings margins, colour, shape ,size, cup disc ratio ,disc edema and pale disc evaluation, any haemorrhages, exudates, vessels details and general fundus .

6) SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY:

Optic nerve head and Macular scans

Subjects eyes were scanned with Spectral Domain Optical Coherence Tomography (SD-OCT, CIRRUS HD OCT MODEL 500). Optic disc and RNFL analysis was derived from Optic Disc Cube 200x200 scans which provide information of size, cup, disc ratio, rim area & volume and circumpapillary RNFL thickness by acquiring a series of 200 horizontal scan lines each composed of 200 A-Scans. The deduced values were reported using a colour pattern where cool colours represent thinner areas and warm colours represent thicker areas. The parameters recorded for this study were RNFL OU Analysis, average RNFL thickness and that in individual four quadrants namely superior, inferior, nasal & temporal were derived in microns (μm).

Macular cube 512x128 measures macula through a square grid of 6mm x 6mm square grid by acquiring a series of 128 horizontal scan lines each composed of 512 A-scans and a central horizontal HD B-scan. The recorded values were represented in a similar colour coded fashion as that of ONH and RNFL. For quantitative interpretation, the macula (6mmx6mm) is divided into nine regions as mentioned in the Early Treatment Diabetic Treatment Study (ETDRS) template by a central ring, i.e., foveal region (1mm diameter), an inner (3mm diameter) and outer ring (6mm), ganglion cell layer assessment was also done under average GCL+IPL thickness in μm and in sectors superotemporal, superior, superonasal, inferonasal, inferior and inferonasal. All scans were obtained single handed, reviewed for image quality and the best quality scan was chosen for the evaluation.

3. RESULTS

Male patients showed dominance (68%) in EON patient. The mean age of presentation was 50±14 years. Sixteen percent (8) eyes presented with severe visual loss, 44 %(22) eyes showed moderate vision loss, 30% (15) eyes with mild visual loss, 10 %(5) eyes were blind.

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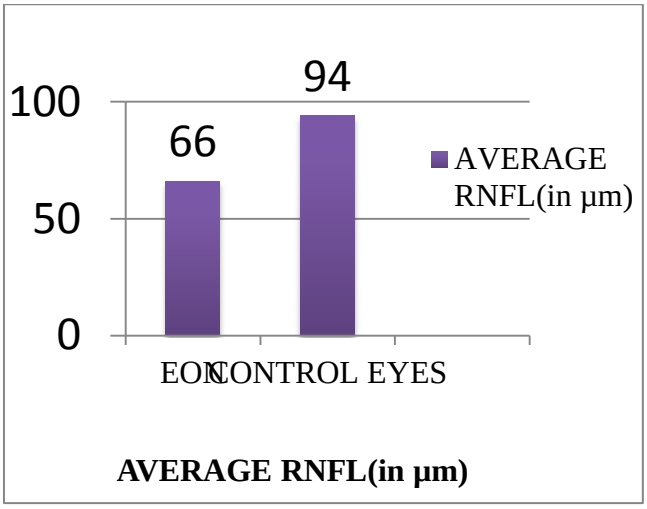
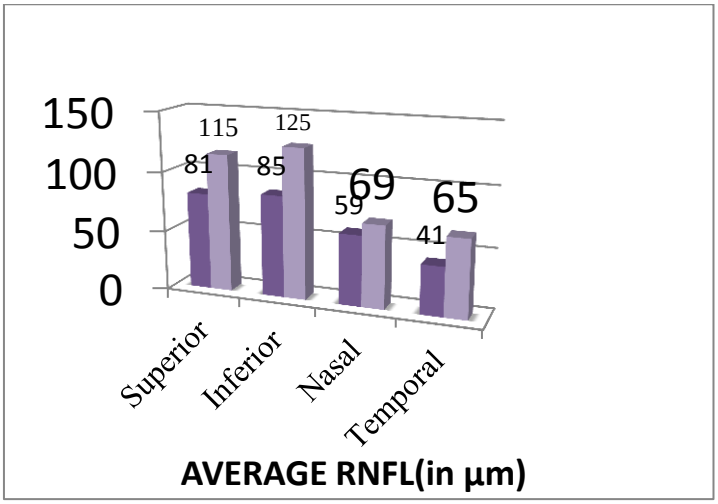
Thirty percent (15) eyes were colour deficient, 8% (4) eyes were colourblind, rest were within normal limit.On visual field assessment, central and cecocentral field defects were 25% and 20%, rest within normal limit. Fundus examinations showed 5% of eyes were pale disc, 15% eyes were with temporal pallor, rest were in normal limits. Mean ±SD value of Average RNFL thickness in EON patients (20%) and in healthy controls were 66.00±10.24µm, 94.23±12.23 µm respectively (p<0.0001)rest patients show RNFL thickness within normal range. In EON patient, the quadrant RNFL thickness was significantly decreased in temporal quadrant (41.55±9.73 µm) and in control group 65.23±10.99 (p<0.01).





Average GCL±IPL thickness were 64.12±10.22 µm in EON, 83.30±8.32 µm in control group (p<0.0002).

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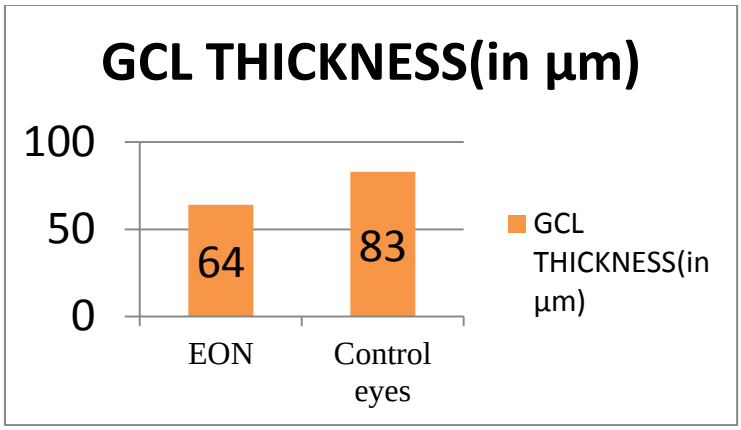

Statistical analysis –Unpaired t test.

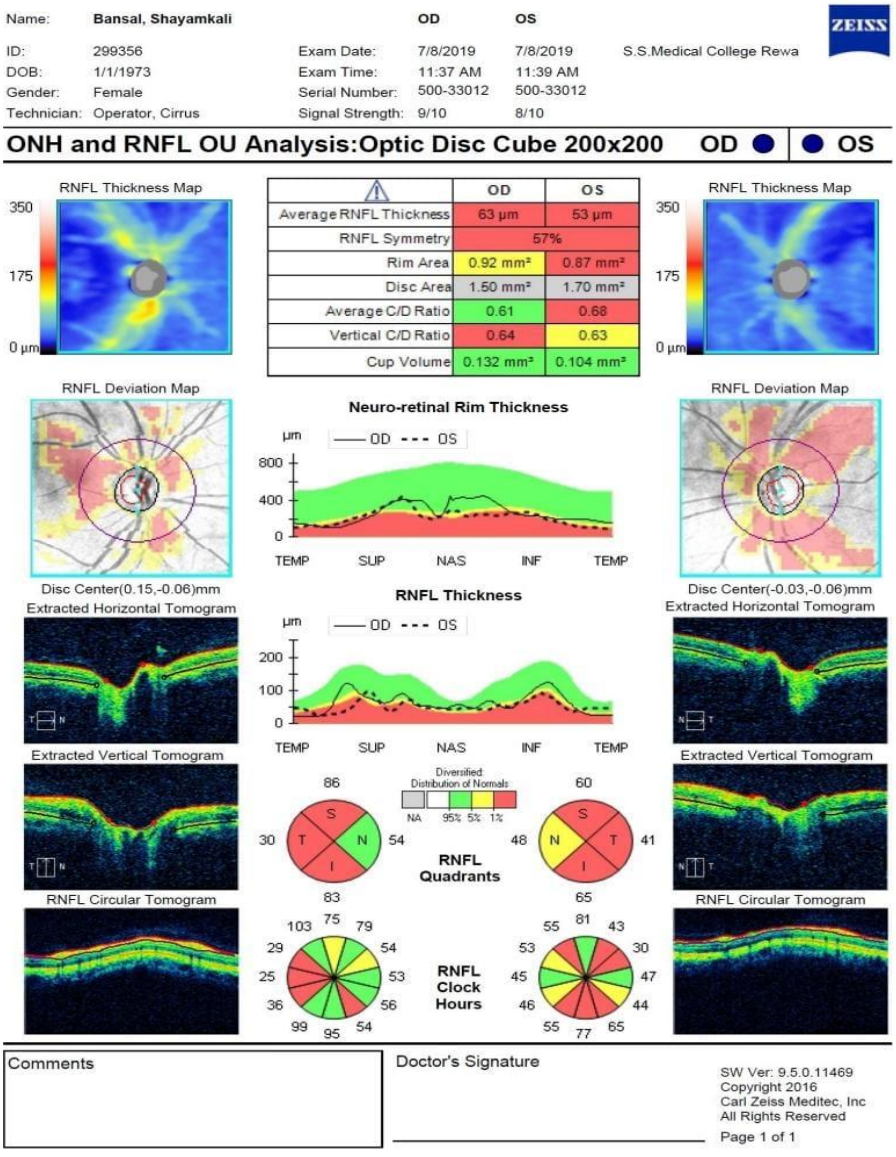

Figure 1.BILATERAL TEMPORAL RNFL THINING IN PATIENTS OF EON

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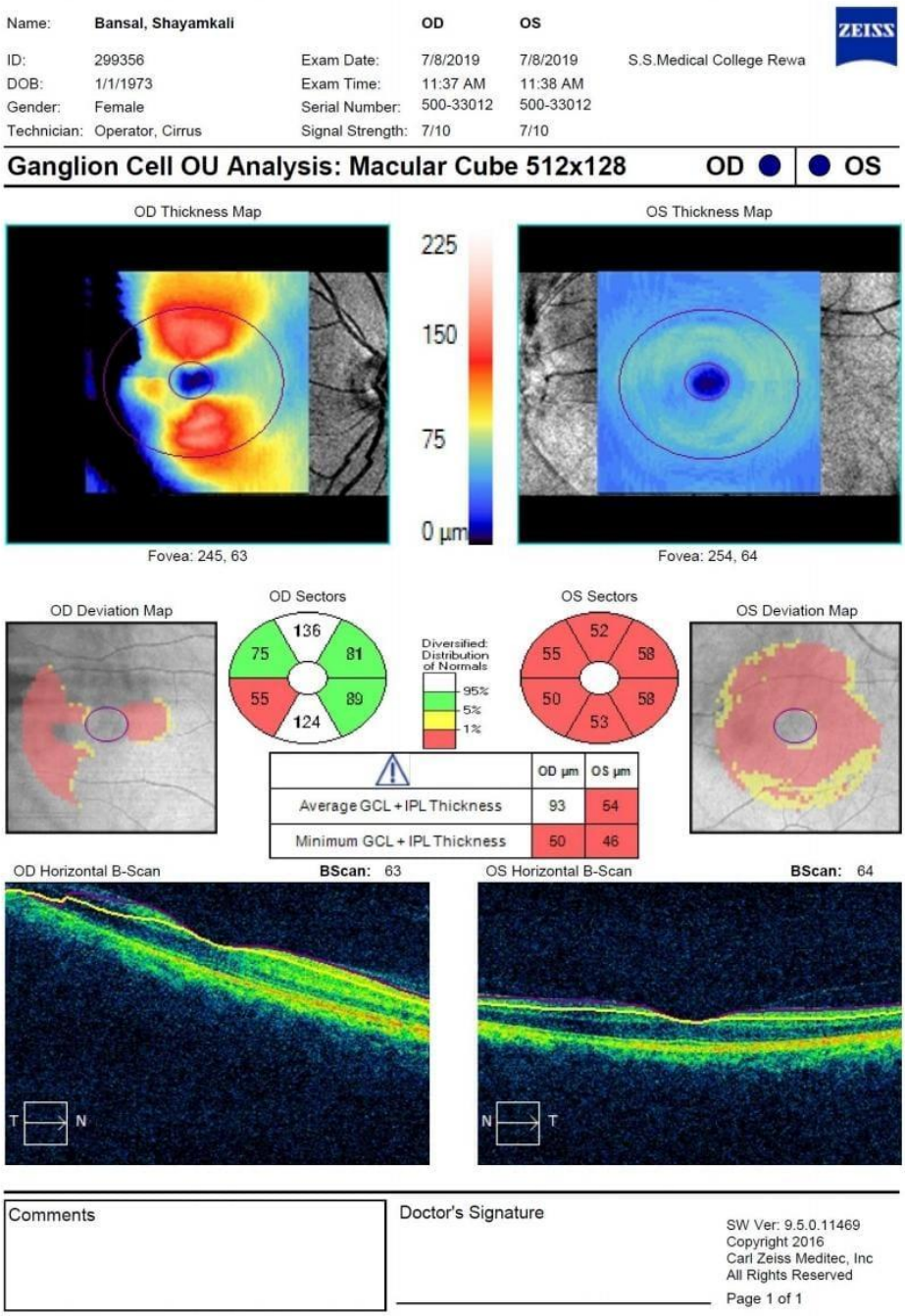

Figure 2.BILATERAL GANGLION CELL THINING IN EON PATIENT

4. DISCUSSION

Tsai et al observed in their study the mean age of EON patient was 59. 6 ±12 years (range, 33–77 years) **[9].**In our study the mean age of EON patient was 50±14 years.

Lee et al observed the symptoms at the first visit were gradual decrease in visual acuity in 15 (72%) patients, visual field constriction in 3 (14%) patients, and dyschromatopsia in 3 (14%) patients **[13].**In our study sixteen percent eyes presented with severe visual loss, 44% eyes showed moderate vision loss, 30% eyes with mild visual loss,10% eyes were blind. Thirty

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percent eyes were colour deficient, 8% eyes were colourblind rest were within normal limit.On visual field assessment, central and cecocentral field defects were 25% and 20%,rest within normal limit. **Grzybowski A et al** noticed the most commonly reported visual field defect in cases of ethambutol-induced toxicity was central or ceco-central scotoma **[14].** Fundus examinations showed 30% of eyes were pale disc,50% eyes were with temporal pallor,rest were in normal limits. Thick RNFL measurements suggest swelling of the retinal nerve fiber layer axons, possibly due to axoplasmic stasis.**[10] .Zoumalan et al**. observed 79% of mean loss in temporal cpRNFL thickness, and the proportion of nerve fiber loss was greater in temporal cpRNFL thickness than in nasal, inferior, and superior cpRNFL thickness in subjects with acute and persistent vision loss. The pattern of RNFL thickening in this study showed that the temporal and inferior quadrants were most frequently affected. **[15]**

The average RNFL thickness was decreased (66.00±10.24µm) in patients of EON and in healthy controls was 94.23±12.23 µm respectively ($p<0.0001$) significantly in our study. In our study we found temporal quadrant showed severe thinning (41.55±9.73 µm) and in control group 65.23±10.99 ($p<0.01$). **Grzybowski A et al, Zoumalan et al, Kardon et al ,Kim et al** observed in their retrospective OCT-based studies on RNFL thickness have similarly reported decreases in temporal RNFL thickness over the course of long-term follow ups compared with the baseline or healthy controls after ethambutol-induced optic neuropathy **[14–17].**

It was observed in the study ,the average GCL±IPL thickness were 64.12±10.22 µm in EON, 83.30±8.32 µm in control group ($p<0.0002$).**Viera et al.[**18] reported a 34% to 40% decrease in the thickness of the retinal ganglion cell layer (compared with a control group) in eight patients with EMB-induced and nutritional optic neuropathy.

5. CONCLUSION

A decrease in RNFL thickness was observed in all quadrants in patients with ethambutol induced optic neuropathy, but more pronounced in temporal quadrant. Decrease in the thickness of the retinal ganglion cell layer should be monitored. Hence careful use of ethambutol must be analysed. Early EOT detection and immediate termination or dose adjustment or alternatives can be used.OCT can evaluate the axonal damage by quantative analysis, severity of visual impairment by measuring RNFL and ganglion cell layer and may predict the visual outcome.

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