

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

## ABSTRACT

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

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

## INTRODUCTION

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

continuous phase in all patients and EMB was administered at a dose of 15 mg/kg/day. In the new regime of ATT, patients

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

### Aims and objectives

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

### MATERIALS AND METHODOLOGY

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

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

direct ophthalmoscopy. Optic disc findings were recorded as pink or pale neuroretinal rim (NRR).

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

### RESULTS

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

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

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

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

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

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

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

Correlation of ONH-RNFL thickness with age and weight is depicted in Table 2. Mean ONH-RNFL values are given in Table 3. Younger patients had lower RNFL values. Patients who weighed less had more ONH-RNFL loss, which was statistically

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

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

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

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

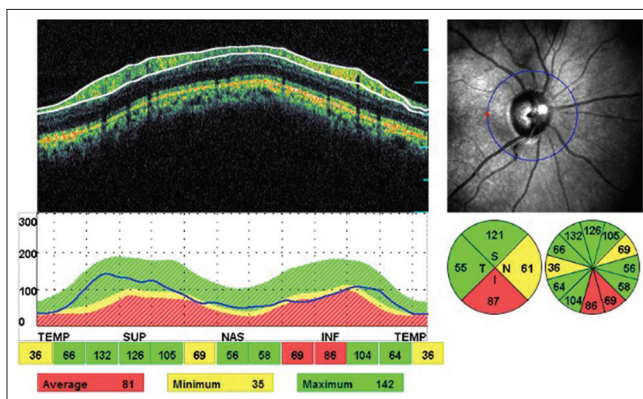


Figure 1: Spectral domain optical coherence tomography image of patient showing retinal nerve fibre layer thinning on optic nerve head-retinal nerve fibre layer scan

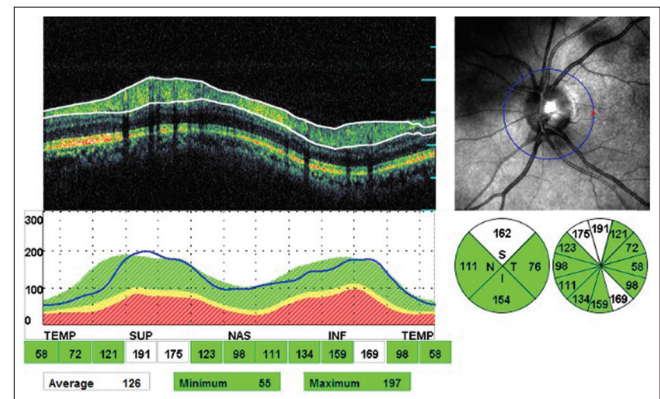


Figure 2: Spectral domain optical coherence tomography image of patient showing retinal nerve fibre layer thickening on optic nerve head-retinal nerve fibre layer scan

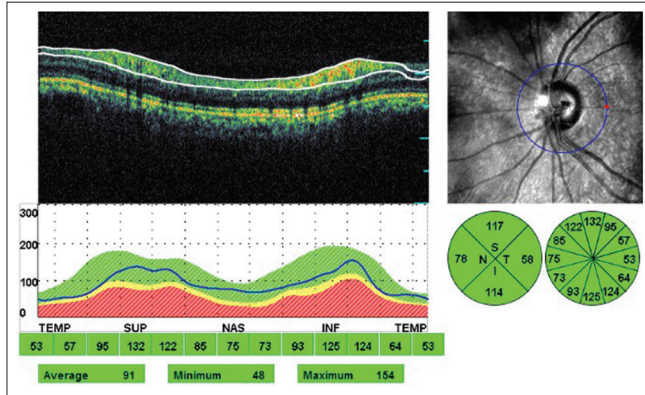
Table 1: Mean values of ethambutol dose across different weight bands

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

<sup>\*</sup>Number of eyes



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



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

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

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

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

<sup>†</sup>Pearson correlation

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

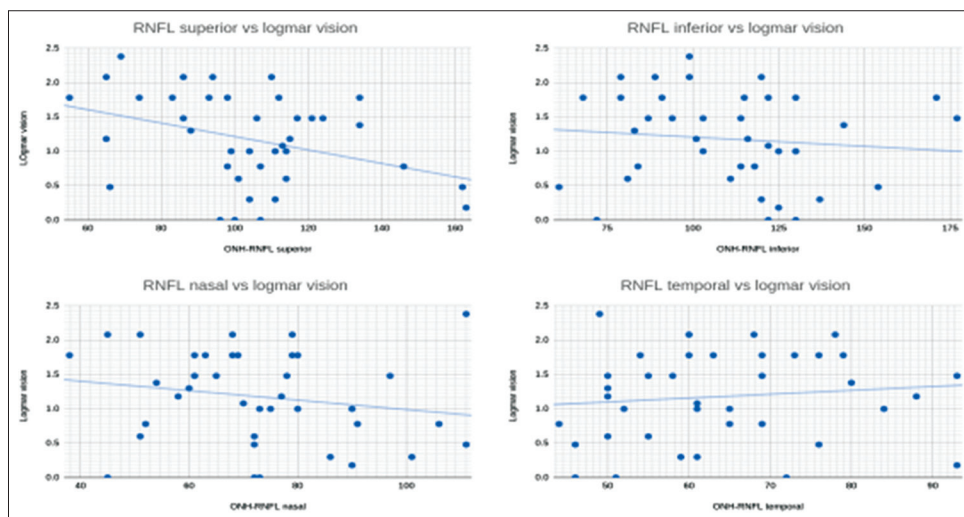
Variable	Value	<i>n</i> *	Superior quadrant* ( $\mu$ m)	Inferior quadrant* ( $\mu$ m)	Nasal quadrant* ( $\mu$ m)	Temporal quadrant* ( $\mu$ m)
Gender	Male	10	111.2 $\pm$ 28.7	118.4 $\pm$ 30.4	75.9 $\pm$ 20.3	64.6 $\pm$ 15.3
	Female	10	96.6 $\pm$ 17.4	103.6 $\pm$ 20.4	69.6 $\pm$ 15.3	63.2 $\pm$ 11.2
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

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

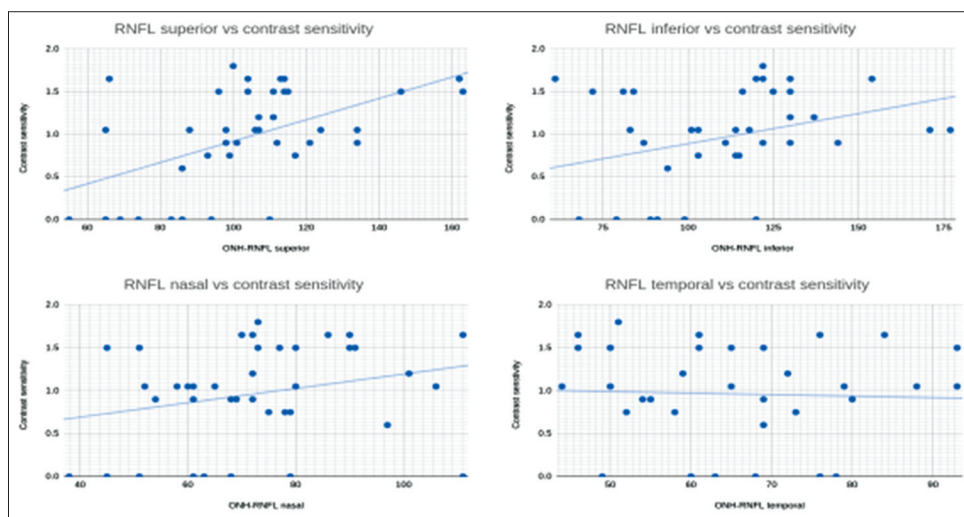
**Table 4: One-way ANOVA test to compare mean optic nerve head-retinal nerve fiber layer thickness in 4 quadrants across different weight bands**

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

\*Number of eyes, <sup>‡</sup>Mean ONH-RNFL thickness. ONH-RNFL - Optic nerve head-retinal nerve fibre layer



Graph 1: Scatterplot chart of optic nerve head-retinal nerve fiber layer thickness versus Logmar vision. x axis- optic nerve head – retinal nerve fibre layer thickness in  $\mu\text{m}$ . y axis - logmar vision



Graph 2: Scatterplot chart of optic nerve head-retinal nerve fiber layer thickness versus contrast sensitivity. x axis- optic nerve head – retinal nerve fibre layer thickness in  $\mu\text{m}$ . y axis - contrast sensitivity value

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

Mean ONH-RNFL values as obtained in each quadrant when analyzed in relation to color vision, pupillary

reaction, and color of the neuroretinal rim are depicted in Table 3.

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

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

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

## DISCUSSION

EMB hydrochloride was introduced as a chemotherapeutic agent in tuberculosis in 1961. The mechanism of action of EMB is believed to be an alteration of the mycobacterial cell wall structure.<sup>[3,4]</sup> EMB has an established place as a first-line antituberculosis agent, valued for the protection that it offers companion drugs against the development and consequences of drug resistance. The ocular side effects of EMB include optic neuritis,<sup>[5]</sup> Red-green color blindness<sup>[6]</sup> and vertical nystagmus. Retrobulbar neuritis is the most common type of

optic neuritis seen. Clinically, EMB-induced optic neuropathy presents with simultaneous bilateral involvement. However, the onset may be unilateral, but eventually, both eyes are involved. The gradual onset and slow progression of the symptoms may delay detection with a consequent delay in management.

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

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

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

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

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

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

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

The effect of various risk factors on ATT-induced ocular toxicity was analyzed by quantifying the ONH-RNFL loss in each group. Age and weight had a positive correlation with ONH-RNFL. Younger age and lower weight were associated with more RNFL loss. Patients at the lower end of the weight spectrum had more thinning of ONH-RNFL. This could be because in the current dosage regimen, a patient weighing 25 kg receives 550 mg of EMB/day, which comes up to 22 mg/kg/day, while a patient weighing 39 kg receives the same 550 mg accounting for 14.10 mg/kg/day. Hence, patients at the lower end of weight band receive a higher dose of EMB. This coupled with the more prolonged duration of treatment with EMB produces a higher cumulative dose in these patients. On analyzing the daily dose per kg body weight in our study, it was found to be  $> 15$  mg/kg body weight in patients belonging to all weight bands. The patients with an abnormality on OCT had received EMB for a longer duration and received a higher cumulative dose of EMB. Patients with extra-pulmonary TB received EMB for a longer duration and had more RNFL loss as compared to those with pulmonary TB. Age, duration of EMB, and dose of EMB were positively correlated with the risk of toxicity in a study conducted by Talbert Estlin and Sadun.<sup>[15]</sup> Medication duration was shown to be a strong risk factor for the occurrence of subclinical toxicity in a study by Jin *et al.*<sup>[16]</sup>

Mean RNFL loss was less in diabetics and hypertensives and more in patients with renal disease, history of smoking and alcoholism. Age, hypertension and renal diseases were risk factors for optic neuropathy in the Taiwanese population in a study by Chen *et al.*<sup>[17]</sup> A low dose and prompt discontinuation of the drug was recommended, particularly in individuals with diabetes mellitus, glaucoma or who are heavy smokers.<sup>[18]</sup> Study by Kanaujia *et al.* concluded that EMB should be avoided in renal disorder patients in view of the high incidence of toxic optic neuropathy.<sup>[19]</sup> Renal failure prolongs the elimination half-life of EMB and increases the risk of EMB-induced optic neuritis. EMB toxicity has been identified as being dose-related, with a reported incidence of 18% in patients receiving  $> 35$  mg/kg/day, 5%–6% with 25 mg/kg/day, and  $< 1\%$  with 15 mg/kg/day of EMB, for more than 2 months.<sup>[20]</sup>

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

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

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

## CONCLUSIONS

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



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

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### Conflicts of interest

There are no conflicts of interest.

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