Prospective study to evaluate incidence and indicators for early detection of ethambutol toxicity

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ABSTRACT

Aims To evaluate incidence of toxic optic neuropathy in patients receiving ethambutol (EMB) for 6 months and to identify its early indicators.

Methods We included 50 patients on anti-tubercular therapy (ATT) including EMB (HRE regimen) based on total body weight for 6 months. Best-corrected visual acuity (ETDRS), colour vision (Ishihara pseudo-isochromatic plates), contrast sensitivity (Pelli-Robson chart), Humphrey visual field analysis (HVF 30-2 SITA FAST), pattern visual evoked response (VER) and spectral-domain optical coherence tomography (SDOCT) for ganglion cell inner plexiform layer (GCIPL) and retinal nerve fibre layer (RNFL) analysis were assessed at baseline and at 2, 4 and 6 months after starting ATT.

Results Mean age of the patients was 36.5±14.7 years with male:female ratio of 2.5:1. Mean daily dosage of EMB was 17.5±1.3 mg/kg/day. No significant change was observed in visual acuity, contrast sensitivity, color vision and mean or pattern SD on HVF at 6 months. Significant increase in VER latency of >2 SD (>125 ms) was observed in 46% eyes on follow-up indicating subclinical toxicity. Significant loss of mean RNFL (from 100.79±16.05 µm to 89.96±13.79 µm) and GCIPL thickness (from 83.1 ±5.60 µm to 79.85±6.45 µm) was observed at 6 months (p=0.001 for both). Patients with subclinical toxicity had significantly greater damage in temporal RNFL quadrant, supero-nasal and infero-nasal GCIPL sectors compared with others.

Conclusion The incidence of clinical EMB optic neuropathy was <2%, though subclinical damage in the form of increase in VER latency, and decrease in RNFL and GCIPL on OCT was seen in 46% eyes.

INTRODUCTION

Tuberculosis (TB) is an important infectious disease and a leading cause of death worldwide. With an estimated 2.75 million cases, India is home to the largest number of TB cases accounting for 27% of global burden.[1] To combat this enormous problem a Revised National Tuberculosis Control Programme was implemented throughout the country under which a thrice weekly intermittent regimen of anti-tubercular therapy (ATT) was shifted to daily dosage regimen in line with WHO recommendation in 2016.[2] It also extended the duration of ethambutol (EMB) intake from 2 to 6 months, leading to a markedly increased cumulative dose of the same.

Although the drug-related visual impairment of EMB was recognised soon after its introduction in 1960s, it still remains a major cause of toxic optic neuropathy.[3] Studies report an incidence of 5–6% with 25 mg/kg/day, 3% with 20 mg/kg/day and 1% with 15 mg/kg/day.[4 5] The toxicity is known to be dose and duration dependent and usually presents between 4 and 12 months of starting the therapy.[6] While ethambutol optic neuropathy (EON) is reported to be reversible, complete recovery may not always be possible resulting in permanent visual impairment.[7 8] The degree of reversibility depends on early recognition of ocular signs and symptoms; thus, detection of visual impairment at an early and subclinical stage is critical.[9]

The aim of the current study was to evaluate the incidence of EMB-related toxic optic neuropathy and identify early markers of the disease.

MATERIAL AND METHODS

Study design

This prospective observational study recruited 50 patients (100 eyes) ≥18 years of age with newly and definitely diagnosed pulmonary or extrapulmonary tuberculosis in the TB clinic of a tertiary care centre who were advised treatment with first-line ATT for 6 months as per the total body weight band—HRZE [isoniazid (H), rifampicin (R). pyrazinamide (Z), ethambutol (E)] for 2 months followed by HRE for next 4 months (table 1).[2]

Therefore, all recruited patients were advised EMB for at least 6 months. Cases with best-corrected visual acuity <0.00 Log MAR, ocular/central nervous system TB, presence of any systemic disease or use of any other drugs known to cause optic neuropathy or any ocular pathology that could affect the parameters that were being evaluated were excluded. The study was approved by the institution review board of our hospital and adhered to the tenets of the declaration of Helsinki. Written informed consent was obtained from all patients recruited in the study. The patients were administered ATT under supervision which ensured 100% compliance with the therapy.

Baseline evaluation

Baseline evaluations were performed prior to starting ATT which comprised a detailed clinical history of present illness, occupation, smoking and among others, along with a complete general physical and systemic examination. Ophthalmic examination included cycloplegic refraction, assessment of pupillary reactions, detailed anterior segment evaluation under slit-lamp and posterior segment evaluation using direct and indirect ophthalmoscopy to rule out ocular TB or any other pathology. Intraocular

Table 1 Drug dosage for adult TB according to total body weight bands

Weight category (total body weight, kg)	Tablets (n)	
	Intensive phase (2 months) H/R/Z/E 75 mg/150 mg/400 mg/ 275 mg	Continuation phase (4 months) H/R/E 75 mg/150 mg/275 mg
25–39	2	2
40–54	3	3
55–69	4	4
≥70	5	5

H, isoniazid, R, rifampicin, Z, pyrazinamide, E, ethambutol; TB, tuberculosis.

pressure was measured using Goldmann's applanation tonometer (Haag Streit AT 900, Koeniz, Switzerland). The specific ophthalmic tests done with the appropriate spectacle correction were best-corrected visual acuity (BCVA) on ETDRS chart (Precision Vision, Woodstock, Illinois, USA) at 4 m, colour vision using Ishihara pseudoisochromatic plates 38 plates edition (Kanehara Trading, Tokyo, Japan) at 33 cm, contrast sensitivity using the Pelli–Robson chart (Precision Vision, Woodstock, Illinois, USA) at 1 m, Humphrey visual field analysis (HVF) 30-2 SITA FAST (Humphrey visual field analyzer Model no. 750i, Carl Zeiss Meditec, Dublin, California, USA), pattern visual evoked response (VER) using (MonPack One Metrovision, France) visual stimulator and monitor and spectral-domain optical coherence tomography (SDOCT) (Cirrus High-Definition Optical Coherence Tomographer Model no. 5000, Carl Zeiss, Meditec, Dublin, California, USA) to evaluate peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion cell inner plexiform layer (mGCIPL) thickness. Monocular, whole-field stimulation with a chequerboardpattern was used to assess the pattern VER. OCT scans were taken after dilating the pupils (at least 5 mm) of both eyes using tropicamide 1% eye drops. pRNFL thickness was assessed using optic disc cube 200*200 protocol using the 'Fast RNFL thickness' protocol. pRNFL thickness was measured in four quadrants. The quadrantic and average RNFL thickness was noted separately for both eyes. mGCIPL thickness was measured in 6 sectors using macular cube 500*128 protocol. The sectoral, minimum and average mGCIPL thickness was noted separately for both eyes. All measurements were repeated on follow-up at 2, 4 and 6 months after starting ATT.

Identifying subclinical toxicity

Subclinical toxicity was defined as the lack of detectable clinical symptoms or signs, but with significant changes on VER which were defined as those showing an increase in the VER latency value greater than 2 SD from the baseline, as in a previous report by Menon *et al*[10] and KW Jin *et al*.[11] Mean baseline VER latency was 115.4±10.1 ms (VER latency at baseline ranged from 104.6 to 126.3 ms). Therefore, any patient with VER latency of >125 ms (ie, >2 SD) at 2nd or 4th months of follow-up were grouped into subclinical toxicity and those with ≤125 ms were grouped into no subclinical toxicity.

Statistical analysis

The data were analysed using statistical software IBM SPSS 24. The quantitative data were expressed as mean±SD and median (minimum and maximum) which followed normal and skewed distribution, respectively. The categorical data were expressed as frequency and percentage. Change in clinical parameters over a time period was assessed by repeated measures analysis of variance followed by Bonferroni multiple comparison test. P value less than 0.05 was considered statistically significant.

RESULTS

Of 50 patients enrolled in the study, 36 were males and 14 were females. The mean age of the study group was 36.4±14.7 years (range 19–70 years). Almost three fourths of the patients (75%) belonged to the age group of 19–49 years. Nearly, all were diagnosed with pulmonary involvement (98%) except one (2%) that had uterine TB. The mean total body weight of the cohort was 67.0±9.7 kg and based on the weight, the mean daily dosage of EMB administered was 17.5±1.3 mg/kg.

None of the patients noticed diminution of vision or any other subjective ocular complain during the study. No change in the fundus or the intraocular pressure was observed at any point of time during the study. Table 2 summarises the results of various parameters at baseline and 2, 4 and 6 months follow-up as seen in 100 eyes. All the patients had BCVA of 0.00 Log MAR and were able to read all cards of Ishihara test type at baseline and on every consecutive visit implying no change in visual acuity and colour vision. No significant change was noted for contrast sensitivity (baseline 1.58±0.22; 6 months 1.56±0.23; p=0.882) throughout the study period. None of the patients developed any visual field defects like enlargement of blind spot or new onset scotoma during any of the follow-up visits. However, a change in mean deviation (from baseline of −5.94±5.33 dB to −4.17±3.05 dB at 2 months) and pattern SD (from baseline of 4.15±2.68 dB to 3.28±2.09 dB at 2 months) parameters of HVF were noted on consecutive visit. This was possibly attributable to the learning curve of the patients.

The pattern VER showed gradual increase in the mean latencies of P100 wave in consecutive visits which was statistically significant (from baseline of 115.4±10.1 ms to 120.3±12.4 ms at 6 months; p=0.001). Similarly, VER amplitude displayed a gradual but not statistically significant decrease from baseline (11.6±5.7 µV) to 6th month (10.5±5.4 µV) of therapy.

The pRNFL thickness significantly decreased from mean baseline values of 100.8±16.1 µm to 89.9±13.8 µm at 6 months (p=0.001). Similar trend was observed in every quadrant as summarised in table 3. The mGCIPL thickness also showed a significant decrease from the baseline mean of 83.1±5.6 µm to 79.8±6.4 µm at 6 months (p=0.001). The minimum mGCIPL thickness and the sectoral values also paralleled the decreasing trend as seen in the overall mean mGCIPL (table 3).

Table 2 Serial measurement of visual functions in 100 eyes

	Baseline	2 months	4 months	6 months
Contrast sensitivity	1.58±0.22	1.56±0.23	1.56±0.24	1.56±0.23
P value		0.069	0.731	0.882
Mean deviation (dB)	−5.94±5.33	−4.17±3.05	−3.50±3.10	−3.11±3.13
P value		**0.001**	0.213	0.754
Pattern SD (dB)	4.15±2.68	3.28±2.09	2.79±1.80	2.47±1.55
P value		**0.001**	0.526	0.764
VER latency (ms)	115.4±10.1	118.2±12.4	119.1±10.4	120.3±12.4
P value		0.068	0.406	0.114
VER amplitude (µV)	11.6±5.7	10.6±4.8	9.9±4.8	10.5±5.4
P value		0.069	0.070	0.180

Bold values signify statistically significant values. VER, visual evoked response.

Table 3 Serial measurement of retinal nerve fibre layer and ganglion cell inner plexiform layer analysis by cirrus high-definition spectral-domain optical coherence tomography (SDOCT)

	Baseline	2 months	4 months	6 months
Retinal nerve fibre layer thickness (µm) (mean±SD)				
Average	100.8±16.1	95.2±13.5	94.0±17.9	89.9±13.8
P value		**0.001**	0.435	**0.008**
Inferior	126.1±24.6	122.1±22.8	118.9±21.4	115.9±21.5
P value		0.072	**0.036**	**0.001**
Superior	129.8±24.9	120.8±22.9	118.1±20.9	113.5±22.9
P value		**0.001**	**0.035**	**0.001**
Nasal	79.5±27.1	74.2±16.1	72.6±13.6	71.1±13.6
P value		**0.036**	0.073	**0.007**
Temporal	67.9±22.5	64.4±13.1	62.4±13.2	59.6±15.1
P value		0.074	**0.003**	**0.001**
Ganglion cell inner plexiform layer thickness (µm) (mean±SD)				
Average	83.1±5.6	81.9±4.7	80.7±5.1	79.8±6.4
P value		**0.001**	**0.001**	**0.011**
Minimum	79.1±6.5	77.8±5.5	76.4±6.7	75.7±7.3
P value		**0.001**	**0.025**	0.822
Superior	83.8±6.1	82.6±5.4	81.9±5.4	80.4±7.6
P value		**0.001**	**0.002**	**0.002**
Supero-nasal	85.4±6.1	84.1±5.6	83.2±5.8	82.3±7.5
P value		**0.001**	**0.001**	0.058
Infero-nasal	83.7±6.4	82.8±5.7	81.8±5.8	81.1±7.1
P value		**0.002**	**0.001**	0.099
Inferior	81.6±6.1	80.3±5.3	79.3±6.2	78.6±6.5
P value		**0.001**	**0.003**	**0.005**
Infero-temporal	82.4±6.6	81.4±5.8	79.7±7.9	79.5±7.2
P value		**0.002**	**0.004**	0.733
Supero-temporal	81.5±6.1	80±5.3	78.7±6.4	77.6±7.2
P value		**0.001**	**0.002**	**0.021**

Bold values signify statistically significant values.

Table 4 Comparison of RNFL thickness and GCIPL thickness between both groups

	VER latency >2 SD (n=23)	VER latency ≤2 SD (n=27)	P value
RNFL thickness (right eye)			
Average	91.5±12.3	92.4±13.8	0.814
Inferior	118.6±17.9	118.9±19.1	0.951
Superior	114.3±21.7	115.0±18.4	0.902
Nasal	71.1±9.8	76.0±16.9	0.206
Temporal	60.3±10.0	66.2±9.0	**0.035**
RNFL thickness (left eye)			
Average	86.3±15.3	89.6±14.0	0.420
Inferior	113.5±14.5	116.4±24.7	0.624
Superior	108.6±29.4	114.4±26.9	0.473
Nasal	68.7±13.1	69.0±14.0	0.937
Temporal	55.7±12.2	63.3±10.8	**0.023**
GCIPL thickness (right eye)			
Average	80.5±5.0	80.0±5.1	0.760
Superior	80.6±5.9	80.8±5.3	0.897
Supero-nasal	80.3±4.5	83.5±4.8	**0.015**
Infero-nasal	80.4±5.5	83.6±4.8	**0.036**
Inferior	78.9±6.1	79.4±6.0	0.411
Infero-temporal	79.3±6.2	80.5±6.2	0.691
Supero-temporal	76.9±6.6	78.5±5.2	0.343
GCIPL thickness (left eye)			
Average	78.6±9.6	80.2±5.7	0.475
Superior	79.1±11.9	80.8±6.4	0.517
Supero-nasal	79.7±10.6	84.3±4.9	**0.048**
Infero-nasal	79.3±8.6	83.4±5.4	**0.047**
Inferior sector	77.6±8.3	78.5±5.9	0.652
Infero-temporal	78.2±10.1	79.8±6.1	0.496
Supero-temporal	76.4±10.6	78.2±5.7	0.462

GCIPL, ganglion cell inner plexiform layer; RNFL, retinal nerve fibre layer; VER, visual evoked response.
Bold values signify statistically significant values.

Among 100 eyes, 46 eyes showed an increase in VER latency of >2 SD (>125 ms) at 2 months or 4 months follow-up indicating subclinical toxicity. Out of 46 eyes of 28 patients, 18 patients had bilateral involvement and 3 patients recovered spontaneously within the treatment period. Subclinical toxicity with unilateral involvement has been documented in previous studies.[10 11] We compared the daily dose of EMB, mean and quadrant-wise RNFL thickness, and mean and sector-wise GCIPL thickness at 6 months between the eyes with and without subclinical toxicity. Patients who showed subclinical toxicity were on higher daily dose of EMB (18±1.0 mg/kg/day) than those who did not (17.2±1.1 mg/kg/day) (p=0.007). The group with subclinical toxicity was also found to have significantly reduced RNFL thickness in the temporal quadrant (right eye (OD) with toxicity 60.3±10.0 µm, without toxicity 66.2±9.0, p=0.035; left eye (OS) with toxicity 55.7±12.2 µm, without toxicity 63.3 ±10.8, p=0.023) and significantly decreased GCIPL thickness in the supero-nasal sector (OD with toxicity 80.3±4.5 µm, without toxicity 83.5±4.8 µm, p=0.015; OS with toxicity 79.7 ±10.6 µm, without toxicity 84.3±4.9 µm, p=0.048) and infero-nasal sector (OD with toxicity 80.4±5.5 µm, without toxicity 83.6±4.8 µm, p=0.036; OS with toxicity 79.3±8.6 µm, without toxicity 83.4±5.4 µm, p=0.047) as compared with the group without subclinical toxicity (table 4 and figure 1).

DISCUSSION

Ethambutol-induced optic neuropathy (EON) is one of the most common and recognised drug-induced optic neuropathies. As EMB is a key component of many anti-mycobacterial treatment regimens, the number of patients suffering with TB worldwide who may be impacted by EON each year is very high.[12] One of the principle theories behind EON has been its chelating property contributing to neurotoxicity.[13] By causing calcium flux into the mitochondria, EMB inhibits the electron transport chain and ATP production.[14] Another important hypothesis describes the demyelination of optic nerve, chiasma and optic tract as the possible mechanism.[15 16]

In our study, the incidence of clinical EON was less than 2% that corroborates with most of the previous literature reporting the incidence in the range of 1–3%.[4 5 17] But changes suggestive of subclinical damage were evident on the VER and OCT. A significant prolongation in mean VER latency and a significant reduction in pRNFL (mean and quadrantic) and mGCIPL (mean and sectoral) thickness from the baseline values were noted on follow-up. However, none of the patients had any visual complaints or deterioration of visual function parameters,

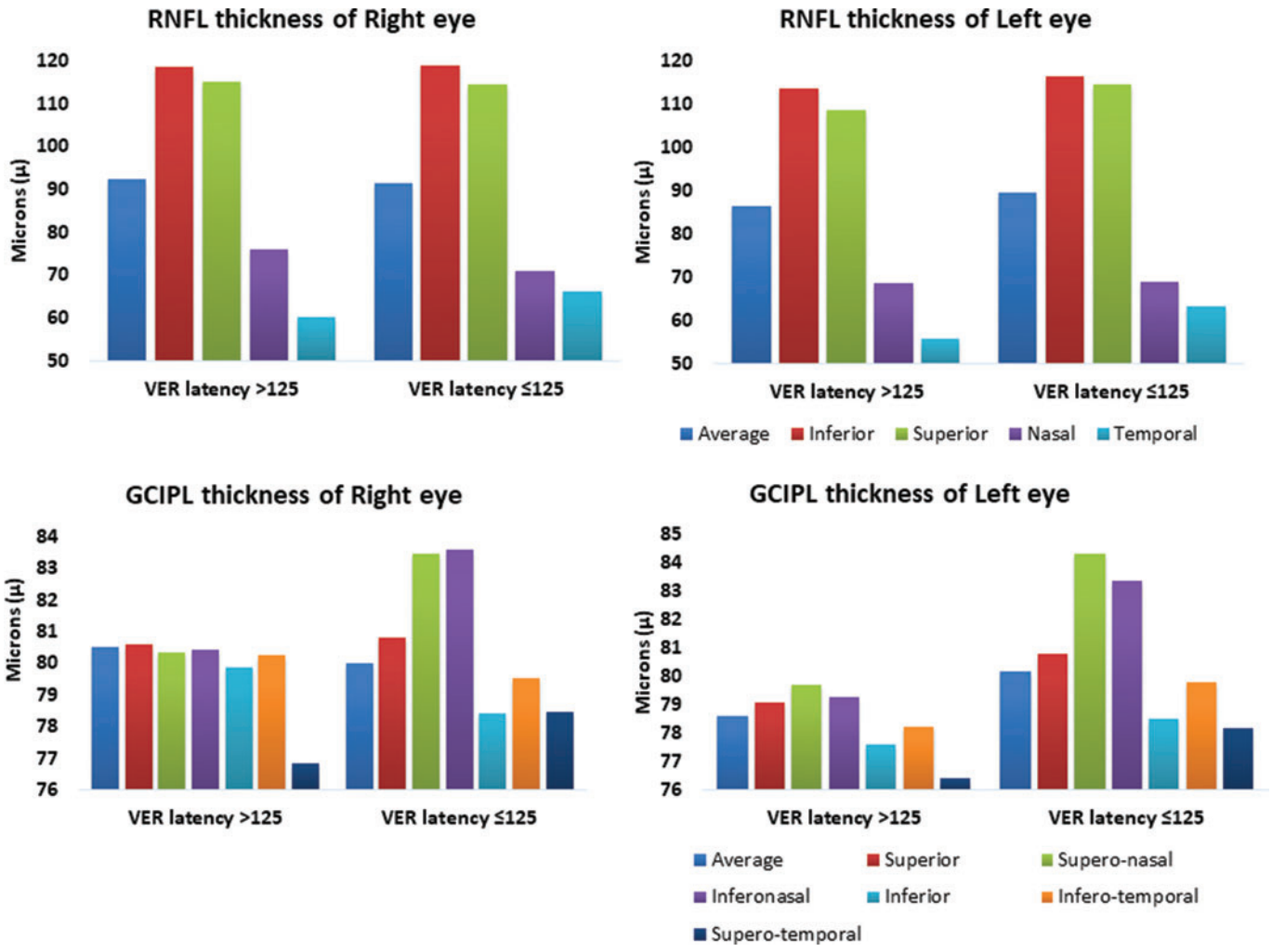

Figure 1 Colour bar diagram comparing retinal nerve fibre layer (RNFL) thickness and ganglion cell inner plexiform layer (GCIPL) thickness between groups with visual evoked response (VER) latency >125 ms and VER latency ≤125 ms of right eye and left eye, respectively.

namely, BCVA, colour vision, contrast sensitivity and visual fields despite these ongoing changes. Similar trend of minimal or no visual complains was noted in other studies despite the subclinical changes.[10 18] This finding does raise concerns about the ongoing quiescent damage at the cellular level related to EMB use which may manifest in the presence of risk factors like renal insufficiency, smoking and old age which were absent in our cohort.

All patients in this study were using EMB in a daily dose of 15–20 mg/kg/day for 6 months based on the total body weight. However, there is a correlation between EMB-induced optic neuropathy and possible overdosing due to dosing on total body weight in obese patients. Obesity can alter the distribution and elimination of various drugs.[19] Since most TB patients lose weight, resulting in a low body mass index, dosing on total body weight usually equals that of ideal body weight.[20]

At this dosage subclinical toxicity was seen in almost half of the eyes (46%) as manifested by the delay in the VER latency of P100 wave. In a previous study, Menon *et al*, demonstrated subclinical damage in nearly 20% eyes on intermittent regimen of 15–20 mg/kg/day for 2 months based on prolongation of VER latency and reduction in mean temporal RNFL thickness and visual field defects.[10] Therefore, daily dose therapy of EMB with greater duration and frequency of administration is likely to be associated with higher incidence of subclinical damage. The pattern VER (latency of P100 wave) appears to be a sensitive and early indicator of EMB toxicity as has been highlighted in various other studies.[10 21 22]

OCT is another important tool that objectively studies the effects of EMB on RNFL.[23–25] Most previous studies conducted prospectively have showed gradual thinning of RNFL over the course of anti-tubercular treatment more significantly in the temporal quadrant of peripapillary RNFL and recommended patients to be followed on serial OCT for early detection of EMB toxicity.[26 27] Lee *et al* have shown that loss of GCIPL thickness indicates an early neuronal loss (earlier than RNFL) and it also predicts the visual recovery after stopping EMB.[28] In this study, we found that a progressive decrease in RNFL thickness paralleled the decrease in GCIPL thickness on consecutive visits in all patients. Hence, OCT appears to be a non-invasive and reproducible technique to pick up subclinical optic nerve damage.

Subclinical toxicity in the form of increased latency of p100 wave of pattern VER was associated with consumption of higher daily dose of EMB (18 mg/kg/day—group with subclinical toxicity; 17.2 mg/kg/day—no subclinical toxicity). Although clinically this difference does not appear to be large, it is important to remember that patients receiving higher doses in the normal range may also be at risk of developing toxic neuropathy.

Our study shows that the functional changes (VER latency) corroborate with the structural changes (noted on OCT) and that incidence of damage to the retinal ganglion cells is very high. Though EON is considered to be reversible in most of the cases, abundant reports of permanent visual damage are there. The risk factors for irreversible visual impairment remain uncertain but old age, renal insufficiency and chronic smoking appears to adversely affect the outcome.[29 30] The absence of these risk factors in our patients could have prevented the development of ostensible EMB toxicity in the presence of structural changes.

Since significant GCIPL and RNFL damage can occur with prolonged use of EMB, it must be used with caution and close monitoring of these patients is mandated. Patient awareness programmes highlighting the risk of EMB toxicity and necessity of reporting to ophthalmologist at earliest sign of decrease in vision are needed. Physicians should also be sensitised about the risk of EMB toxicity and high incidence of subclinical damage in the form of increased VER latency and RNFL damage. Dose titration of EMB is must as patients in the same weight band receiving higher doses of EMB showed more subclinical damage. Special care is indispensable in patients with high risk of toxicity, for example: with renal damage, nutritional deficiency and among others.

There are certain limitations of the study that merit mention. First, we did not appraise the changes after discontinuation of the drug that would have helped assess the reversibility of subclinical toxicity. Furthermore, there is a possibility of missing blue-yellow or early subtle colour vision defects in Ishihara test type and that could have been documented using other colour vision tests like 100 hue tests. Finally, the concurrent effect of isoniazid cannot be ruled out.[31]

In conclusion, a significant structural and functional changes occurred even though the patients on ATT did not show any signs of clinical toxicity. Changes in pattern VER and RNFL and GCIPL thickness analysis on OCT are the earliest markers of subclinical EMB toxicity. Therefore, vigilant administration of EMB dose is extremely vital and patients who are on higher dosage or for prolonged duration of the drug should be assessed regularly using these parameters regardless of the absence of visual complaints. The physicians should also be alerted about the risk of EMB toxicity and the high incidence of subclinical damage.

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