Original Article

Ocular Toxicity among Patients taking Anti-tubercular Treatment

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ABSTRACT

Introduction: Tuberculosis remains a major public health problem in Nepal and anti-tubercular drugs used for the treatment of pulmonary and extrapulmonary tuberculosis can be associated with ocular toxicity. This prospective study aimed to evaluate the incidence of ocular toxicity among patients receiving anti-tubercular therapy and to assess the change in visual functions and ocular imaging before and after use of anti-tubercular therapy.

Materials and methods: A total of 89 eyes of 45 TB patients taking anti-tubercular therapy were enrolled. Detailed history and examination including best-corrected visual acuity (BCVA), colour vision (Farnsworth D-15t), contrast sensitivity (Pelli-Robson chart), Goldman visual field analysis and spectral domain optical coherence tomography for retinal nerve fibre layer (RNFL) analysis were assessed at baseline and at 6 months after starting anti-tubercular therapy. Visual evoked potential (VEP) was performed in suspected cases.

Results: The mean age of the patients was 29.13±14.00 years and 62.2% were males. The mean weight of the subjects was 54.37±10.36 kg, mean daily dosage of ethambutol was 17.91±1.74 mg/day/kg and mean administration duration was 2.71±1.54 months. The incidence of ocular toxicity was 2.24%. Bilateral retrobulbar optic neuropathy occurred in a 27-year female of 55 kg receiving ethambutol (20 mg/kg/day) for 6 months for Pott's spine. Her best-corrected visual acuity in both eyes was reduced to 6/36 from 6/6 and developed non-specific color vision defect, decreased contrast sensitivity, bilateral cecocentral visual field defect and mean decrease in retinal nerve fibre layer thickness compared to the baseline data. In rest cases, a statistically significant decrease in mean retinal nerve fibre layer thickness in both eyes suggested the evidence of subclinical toxicity.

Conclusion: Though less common, ethambutol toxicity can occur in patients under anti-tubercular therapy in the form of retrobulbar optic neuritis. Decreased contrast sensitivity and thinning in the mean retinal nerve fibre layer thickness can be the indicator of subclinical toxicity.

Keywords: Anti-tubercular treatment (ATT), Ethambutol, Optic neuropathy, Optical coherence tomography (OCT), Tuberculosis

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* and is the eighth leading cause of death in Nepal and it remains one of the major public health problems in the country (Nepal Health Research Council et al, 2019). According to the National TB prevalence survey done in 2018-19, around 69, 000 people developed TB in 2018 with an estimated incidence of 245/100,000, which was almost 1.6 times higher than previously estimated (Centre, 2020). TB particularly affects the lungs causing pulmonary TB but can affect other sites as well which is called extra pulmonary TB. The currently recommended treatment for new cases of drug-susceptible TB is a six-month regimen (fixed dose combination) of four first-line drugs: Isoniazid(H), Rifampicin(R), Ethambutol(E) and Pyrazinamide(P) for the 2 months followed by a continuation phase of isoniazid and rifampicin for 4 more months (2HRZE+4HR) under Directly Observed Treatment Strategy (DOTS). For cases with severe forms of extrapulmonary TB or retreatment cases the continuation phase is longer and consists of ethambutol in addition to isoniazid and rifampicin.

Ethambutol is one of the important first-line antituberculosis agents but is associated with ocular toxicity in about 0.5-4.3% (Chen et al, 2015, Lee et al, 2008, Narang and Varma, 1979, Polak et al, 1985, Trusiewicz, 1975). It is reversible in most cases and is related to the dose and duration of treatment, but may occasionally become irreversible resulting in permanent visual disability especially in the older population. Apart from Ethambutol, Isoniazid, though to a lesser extent, has also been implicated in the development of visually related side effects (Jimenez-Lucho et al, 1987, Russo and Chaglasian, 1994).

Ethambutol induced ocular toxicity usually occurs within 15 days to 24 months following commencement of therapy with the mean duration being 3-5 months except in some rare conditions (Chatterjee et al, 1986, Schild and Fox, 1991). The usual symptoms are bilateral progressive painless blurring of central vision or inability to identify colors. But on initial presentation, the fundus may appear completely normal in retrobulbar optic neuritis. Pupillary abnormalities can be subtle, and visual evoked potential may be needed to confirm the diagnosis (Srivastava et al, 1997). The contrast sensitivity measurement has also been found effective in detecting subclinical toxicity (Salmon et al, 1987). Moreover, OCT can help to quantify the loss of retinal nerve fibers of these patients as a sign of early toxicity, before the fundus changes become apparent (Chai and Foroozan, 2007).

Isoniazid induced optic disturbances are less frequently reported and are mainly due to disturbances in pyridoxine metabolism. Apart from the disturbances in visual acuity, color vision and contrast sensitivity; isoniazid induced optic neuropathy has bilateral optic disc swelling. Visual field defect often have the appearance of bitemporal hemianopic scotomas (Sharma and Sharma, 2011).

The prognosis of ATT induced ocular toxicity is variable and is described as dose and duration related and reversible on therapy discontinuation, reversibility of optic neuritis may occur in half to a third of the affected individuals (Chan and Kwok, 2006, Lee et al, 2008). Few studies from abroad have proposed

timely baseline and follow up ophthalmological evaluation for early detection and prevention of severe visual impairments in patients to avoid ocular toxicity (Rao et al, 2006), (Kokkada et al, 2005). We conducted this study to evaluate the incidence and clinical manifestations of ATT induced optic neuropathy in the Nepalese population and to identify the factors that influence the development of these side effects.

MATERIALS AND METHODS

This was a descriptive observational study to examine the ocular status among the newly diagnosed TB patients (pulmonary + extrapulmonary) taking ATT conducted at the ophthalmology department of Institute of Medicine. TB cases above > 18 years who had recently started ATT intake (<1 month) were recruited from 3 different DOTS centres - Tribhuvan University Teaching Hospital (TUTH) DOTS centre, Budhanilkantha health post DOTS centre and Helping Hands DOTS centre. The subjects were recruited by non-probability consecutive sampling from September 2019 to June 2021. Detailed ocular evaluation was done within 1 month of initiation of ATT and follow-up records were obtained at the end of 6 months of ATT. The ocular investigations conducted were Color vision (Farnsworth Dichotomous D-15 test), Contrast sensitivity test (Pelli-Robson contrast sensitivity chart), Goldman visual field test (Takagi company) and Optical coherence tomography (SD-OCT; Spectralis® OCT, Heidelberg Engineering, Heidelberg, Germany) of optic nerve head and 4 quadrants peri papillary retinal nerve fibre layer was performed. Pattern visual evoked potentials (VEP Roland Consult, Denmark) was also done in ethambutol toxicity suspected cases using monocular, whole-field stimulation with a checkerboard pattern. MRI of the brain and orbit was done for cases where as per need. ATT patients who had pre-existing ophthalmologic problems (diabetic retinopathy, visually significant cataract, glaucoma or optic nerve head abnormalities), ocular tuberculosis cases, drug resistant TB cases were excluded.

Ethical approval from the Institutional Review Committee of Institute of Medicine was obtained and informed written consent was obtained from all involved participants. All procedures performed in study were in accordance with the ethical standards and declaration of Helsinki.

The diagnosis of ATT induced optic neuropathy was based on the following criteria: the diagnosis had to satisfy more than 1 of the major criteria and more than 2 of the minor criteria- *Major criteria*: 1) abnormal results on the colour vision test and no other reasonable cause for abnormal colour vision, and 2) central or paracentral scotoma on the Goldmann or Humphrey perimeter. *Minor criteria*: 1) visual field defects other than central or paracentral scotomas, and 2) optic disc pallor.

If ATT induced optic neuropathy was diagnosed, Ethambutol was stopped immediately and physician consultation will be taken regarding the need to start second line therapy. Follow up examination of the subject to see for the reversibility of symptoms at 6 weeks, 3 months, 6 months and 9 months from the time of stopping ATT. If the symptoms continue to worsen even after stopping ethambutol after 1 month, isoniazid was also stopped.

Data entry was done using MS excel and analysis was done using the Statistical Package for Social

Science (SPSS) version 21 by the investigators with the help of a statistician. The incidence of ATT induced optic neuropathy was calculated among the cohort taking ATT during the study period using descriptive statistics. Confidence interval was considered at 95% level. P-value less than 0.05 was considered significant.

RESULTS

A total of 89 eyes of 45 subjects meeting the inclusion criteria were included in our study. The mean age of the TB subject was 29.13±14 years (18-74 years), out of them, 62.2% (n-28) were male and 37.8% (n-17) were female. PTB was present in 44.4% and the rest 55.6% had extrapulmonary TB. (Table 1)

Around 37 cases received the CAT-I regimen of 2HRZE+4HR. Rest for 8 cases who had presented as severe extrapulmonary TB were cases of Pott's spine (n-1), Tuberculous meningitis (n-2), Tuberculous osteomyelitis (n-3) and Tuberculous Pericarditis (n-2) and they received CAT-II regimen of 2HRZE+7-9 HRE.

Detailed ocular examination of the anterior segment was within normal limits in all the patients except for one which had phlyctenular conjunctivitis and two with allergic conjunctivitis which were not related to the ATT toxicity. The pupillary reaction and even the fundus findings were normal in all the subjects. All the ocular findings were documented at the time of presentation (<1 month of ATT) as pre ATT findings and after 6 months of completion of ATT as post ATT findings. Table 2 shows the comparison of visual acuity before and after the use of ATT. Apart from one patient with NPL, all other eyes had best corrected visual acuity of >6/12 with the refractive correction.

The colour vision tests and the pattern of Goldmann visual field analysis were documented at the time of presentation and after the treatment and shown in table 3.

Table 1: Distribution of different categories of tuberculosis based on anatomical site.

Types of tuberculosis	Frequency	Percentage
Pulmonary	20	44.4%
Extra Pulmonary	25	55.6%
Endometrial tuberculosis	1	2.22%
Renal tuberculosis	1	2.22%
Pott's spine	1	2.22%
Tuberculous meningitis	2	4.44%
Tuberculous Pericarditis	2	4.44%
Tuberculous osteomyelitis	3	6.66%
Abdominal tuberculosis	4	8.88%
Tubercular lymphadenitis	11	24.44%
Total	45	100%

Table 2: Visual acuity before and after starting the ATT.

	Pre ATT		Post ATT	
BCVA	**Right Eye**	**Left eye**	**Right Eye**	**Left Eye**
NPL*	0%	1 (2.22%)	0%	1 (2.22%)
6/36	0%	0%	1 (2.22%)	1 (2.22%)
6/12	1 (2.22%)	1 (2.22%)	1 (2.22%)	1 (2.22%)
6/9	4 (8.88%)	2 (4.44%)	4 (8.88%)	2 (4.44%)
6/6	40 (88.9%)	41 (91.11%)	39 (86.68%)	40 (88.9%)

**NPL= No Perception of Light*

Table 3: Visual functions before starting ATT and after the use of ATT.

		Pre ATT		Post ATT	
		Right Eye	**Left Eye**	**Right Eye**	**Left Eye**
Colour Vision Test	Normal	32 (71.1%)	31 (68.9%)	30 (66.7%)	30 (66.7%)
	Non specific	12 (26.7%)	10 (22.2%)	13 (28.9%)	11 (24.4%)
	Tritan	1 (2.2%)	3 (6.7%)	2 (4.4%)	3 (6.7%)
	Could not be assessed	0%	1 (2.2%)	0%	1 (2.2%)
Goldmann Visual Field Test	Normal	36 (80%)	36 (80%)	33 (73.3%)	35 (77.7%)
	Superior Constriction	6 (13.3%)	5 (11.1%)	7 (15.5%)	5 (11.1%)
	Over all Constriction	0%	1 (2.2%)	0%	1 (2.2%)
	Supero nasal Constriction	1 (2.2%)	0%	1 (2.2%)	0%
	Centrocecal Scotoma	0%	0%	1 (2.2%)	1 (2.2%)
	Enlarged Blind Spot	2 (4.4%)	2 (4.4%)	3 (6.6%)	2 (4.4%)
	Could not be assessed	0%	1 (2.2%)	0%	1 (2.2%

Table 4: The comparison of contrast sensitivity before and after ATT use.

Contrast sensitivity (log units)	Pre ATT	Post ATT	95% CI of the difference	P value
Right Eye	1.99±0.17	2.01±0.18	(-0.064-0.02)	0.450
Left Eye	2.00±0.17	1.98±0.23	(-0.03-0.07)	0.488

Table 5: OCT RNFL thickness before and after the use of ATT.

RNFL thickness in various quadrants (µm)	Right Eye				Left Eye			
	Pre ATT	Post ATT	95% CI of the difference (Lower-Upper)	P value	Pre ATT	Post ATT	95% CI of the difference (Lower-Upper)	P value
Superior	137.23±16.86	134.23±17.38	(0.13-5.86)	0.041	140.52±19.13	138.14±18.12	(0.61-4.14)	**0.011**
Inferior	137.00±15.96	136.09±17.36	(-3.60-5.41)	0.680	136.04±16.98	133.85±16.90	(-3.37-7.75)	0.421
Nasal	79.14±15.53	78.38±14.87	(-3.14-4.66)	0.689	76.71±13.81	74.80±15.24	(-2.63-6.44)	0.391
Temporal	67.95±11.11	67.85±7.15	(-4.721-4.91)	0.968	66.57±10.85	67.61±8.10	(-5.11-3.01)	0.597
Mean	105.33±10.92	104.14±10.69	(-0.41-2.79)	0.137	104.96±11.03	103.60±11.25	(-0.41-3.13)	0.127

The mean contrast sensitivity in the right eye was 1.99±0.17 log units (1.50-2.25 log units) and 1.95±0.34 log units (1.55-2.25 log units) in the left eye before ATT. And after ATT, the mean contrast sensitivity in the right eye was 2.01±0.18 log units (1.50-2.25 log units) and 1.98±0.23 log units (1.00-2.25 log units) in the left eye, indicating no significant changes as shown in table 4.

There was a statistically significant decrease in OCT RNFL thickness in the superior quadrant after taking ATT in the BE (Table 5). Although there was a decrease in RNFL thickness in nasal, inferior and temporal quadrants and mean RNFL thickness, the values were not statistically significant in BE.

The mean weight of the subjects in the study was 54.37±10.36 kilogram. The mean daily dose of ethambutol was 17.91± 1.74 mg/day/kg (range: 16.35–20.6) over a mean administration duration of 2.71±1.54 months. The mean daily dose of isoniazid was 4.90±0.42mg/day/kg (range: 4.29-5.63).

The incidence rate of ATT induced toxicity was 2.24% as only 1 patient developed the features of Ethambutol toxicity during our study period.

Ethambutol induced optic neuropathy (EON) in a 27 year old female

In our study there was only 1 case that developed ocular toxicity of ethambutol within the six month follow up period. She was a 27 year old female, a new case of Pott's spine who had received the 4HRZE + 2 HRE treatment. Her body weight was 55 kg and she had received ethambutol dosage of 1100 mg /day (20 mg/kg/day) for 180 days; cumulative dosage of 13,368gm. She did not have any systemic comorbidities and family history was also not significant. Her baseline examination including anterior and posterior segment findings, visual acuity, colour vision, contrast sensitivity and visual fields were all within normal limits. At the 6 month follow up, she complained that she was having painless and gradually progressive diminution of vision in both the eyes since the last 15 days. Ethambutol had been stopped by her treating physician 2 days back.

On her 6 month follow up examination her BCVA was 6/36 in both eyes. The anterior and posterior segment findings were within normal limits and the pupillary reactions were also normal. The optic discs were pink and round with sharp margins (Figure 1 A, B). The colour vision in both the eyes showed non-specific colour vision defects and the contrast sensitivity had dropped to 1.75. Goldman visual fields in both the eyes showed a cecocentral scotoma (Figure 1 C, D). The mean peripapillary RNFL thickness in RE and LE had decreased by 6 and 5 microns from the baseline examination values in OCT. Visual evoked potentials showed delayed P 100 latencies with normal amplitudes in both eyes (Figure 1E). The patient was treated

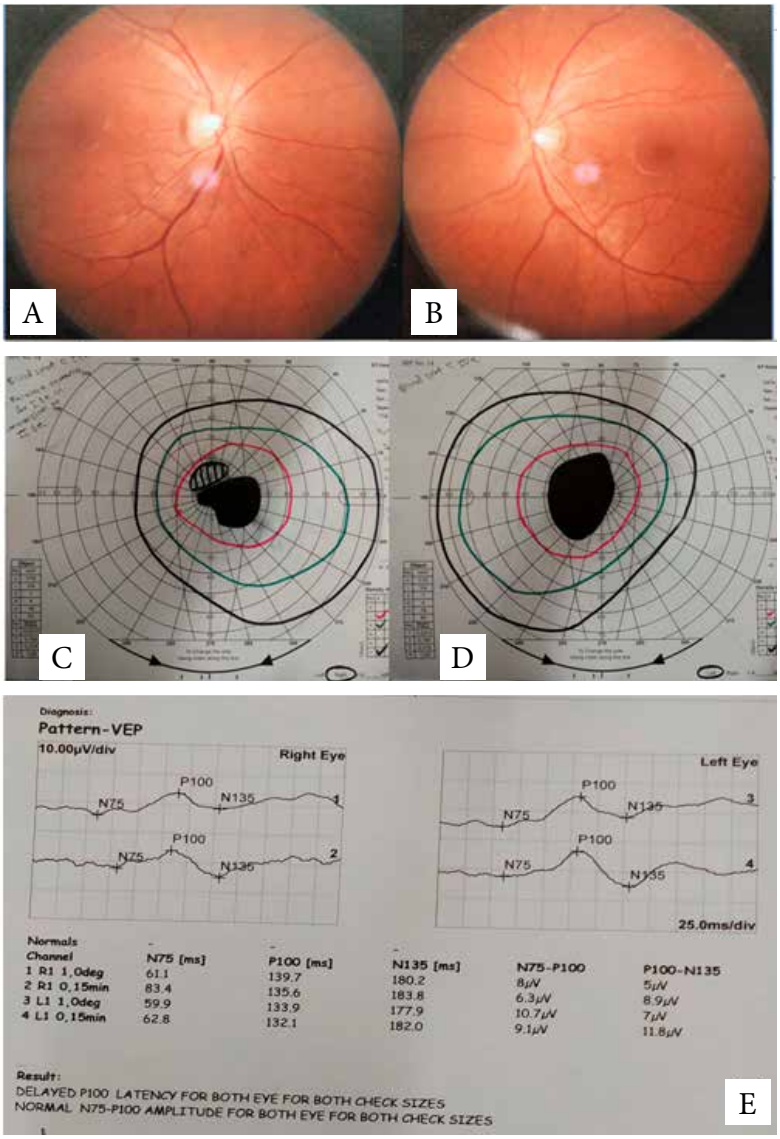

Figure 1: Fundus photo of RE (A) and LE (B) of a 27-year-old female with ethambutol induced optic neuropathy showing normal optic disc and macula. The goldmann visual fields of RE (C) and LE (D) showed constriction of the visual fields with cecocentral scotoma. And the visual evoked potentials showing delayed P 100 latencies with normal amplitudes in both eyes (E).

with multivitamins containing Zinc and copper supplements along with high dosage pyridoxine 100 mg/day for 6 weeks. At 6 weeks follow up the visual acuity had improved by 1 line and the contrast sensitivity had also improved to 1.85.

DISCUSSION

TB is an old disease but continues to remain a major public health problem in many developing countries. TB is one of the top 10 causes of death and the leading cause of a single infectious agent above HIV/AIDS across the world.(Centre, 2019) It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). Currently there is only one category of treatment for TB patients needing first-line treatment- 2 HRZE/4HR. For complicated or severe extrapulmonary TB cases the current regimen is 2 HRZE + 7-10 HRE and for drug- resistant TB (DR-TB), Ethambutol may be required for 6-10 months depending on the resistance pattern.

Ethambutol was first introduced in 1961 as a bacteriostatic agent for Mycobacterium tuberculosis and its ocular toxicity was documented immediately the next year(Carr and Henkind, 1962). Since then numerous reports of ethambutol-induced optic neuropathy have been published in the literature (Citron and Thomas, 1986, Leibold, 1966). The toxicity could be due to decreased levels of copper in mitochondria or from accumulation of zinc in lysosomes of retinal ganglion cells. The most commonly identified type of EMB toxicity has been dose and duration related, with a reported incidence being as high as 18% in patients receiving >35 mg/kg/day, 5-6% with 25 mg/kg/day, and <1% with 15 mg/kg/day of EMB, when receiving for more than two months (Citron and Thomas, 1986, Yee et al, 2003). In our study, the mean ethambutol daily dose of patients developing EON was 17.91± 1.74 mg/kg.

The incidence rate of ethambutol induced ocular toxicity in our study was 2.24% (2/89 eyes) among patients receiving 17.91± 1.74 mg/kg/d for a mean duration of 2.71 ± 1.54 months. This is alike the findings in other Asian countries like in Taiwan where ethambutol toxicity was 1.29% (Chen et al, 2015) and in India (Narang and Varma, 1979) and Korea (Lee et al, 2008), it was estimated to be <2 %. However the actual incidence may be underestimated.

Our patient who had developed ethambutol induced retrobulbar optic neuritis was a 27-year-old female with Pott's spine with normal renal function who had received ethambutol at 20mg/kg/day for a duration of 180 days. Literature has documented severe visual impairment usually in 4-5 months of ethambutol usage (Citron and Thomas, 1986, Leibold, 1966).

Usually the risk of EMT is uncommon for patients receiving first-line ATT as per the national DOTS guidelines. But in severe TB cases, drug resistant TB cases, compromised renal function patients, cases with body weight on the lower end of the weight band and among those receiving a fixed dose combination are at a higher risk of EMT. The dosage received by our case of EMT was slightly higher (20 mg/kg/day) than average as she fell on the lower end of her category of weight band receiving the fixed dose combination (4 tablets for weight range from 55-70 kg). Although fixed dose combination according to weight makes the treatment easy to prescribe, it may be

disadvantageous for the unlucky few who fall on the lower ends of their weight band, thus receiving a higher dosage per kg body weight. And it was the same coincidence for our case of EMT.

However, none of the other patients in our study group had any visual complaints or deterioration of visual function parameters like BCVA, colour vision, contrast sensitivity or Goldman visual fields but there was reduction in RNFL thickness.

Our TB patients mainly belonged to the 3rd decade (mean age 29.13±14.00 years) with a mean weight of 54.37±10.36 kgs and the majority had extrapulmonary TB. Reports support that younger patients are more likely to develop extrapulmonary TB (Pang et al, 2019). But the reports from Korea and India have depicted Ethambutol optic neuropathy (EON) more common in the PTB (Lee et al, 2008, Mandal et al, 2021).

Our patient with EON had subacute bilateral painless gradually progressive blurring of vision with altered colour perception and cecocentral scotoma in Goldman visual field test. The commonly reported visual field defects in literature in cases with EON is cecocentral scotoma but other types of defects like bitemporal defects or constriction of the peripheral field have also been seen (Boulanger Scemama et al, 2013, Chan and Kwok, 2006, Melamud et al, 2003).

In a retrospective study be Lee et al from Korea, 10 out of 13 patients who developed EON were above 50 years and all cases had pulmonary TB being treated with ethambutol for a mean duration of 9.38 ±10.12 months, receiving a daily dosage of 17.85 ± 2.21 mg/kg. India is also a TB endemic country-like ours and a prospective study from India, reported 36.4±14.7 years (range 19–70 years) as the mean age of the ATT patients and 98% had PTB. Although none of their patients developed EON at 6 months, subclinical toxicity was noted in the form of significantly decreased pRNFL thickness and mGCIPL thickness values from baseline and statistically significant increase in the mean latencies of P100 wave in pattern VEP (Mandal et al, 2021).

Subclinical EON is common among ATT patients where there can be a lack of detectable clinical symptoms or signs in the presence of significant changes on VEP (Mandal et al, 2021). Another study defined subclinical toxicity as significant changes in numeric characteristics such as color vision, contrast sensitivity, VF global indices, and RNFL thickness by OCT showing changes were greater than 2 SD from the baseline (Jin et al, 2019).

Automated visual fields are more sensitive to detect subclinical toxicity so the Goldmann visual fields in our study might have missed cases with subclinical EON. The OCT done among our cases showed a significant reduction in peripapillary RNFL (mean and quadrantic-superior, inferior and temporal in RE and superior, inferior and nasal in LE) thickness from the baseline values noted on follow-up. Other previous studies also showed gradual thinning of RNFL over the course of anti-tubercular treatment more significantly in the

temporal quadrant of peripapillary RNFL (Chai and Foroozan, 2007, Jin et al, 2019).

Indian studies have mentioned that though the incidence of EON is low, subclinical damage in the form of increase in VER latency, and decrease in RNFL and OCT can be seen in upto 46% eyes (Mandal et al, 2021). However, Han et al noted thickening of the peripapillary RNFL and thinning of the perifoveal ganglion cell inner plexiform layer (GCIPL) in one patient with EON at the onset of symptoms while the rest of the 36 patients without EON did not have any statistically significant changes in RNFL (Han et al, 2015). The GCIPL thickening indicates an early neuronal loss (earlier than RNFL) and it also predicts the visual recovery after stopping EMB and various studies have found it useful to monitor EON (Boulanger Scemama et al, 2013, Han et al, 2015, Jin et al, 2019). We did not perform the GCIPL thickness measurement due to the lack of this facility in our OCT machine.

In summary, Nepal has been very successful in implementing the DOTS program and the cure rate of TB has improved dramatically after adoption of the STOP TB program. As we move forward with the goal to eliminate TB by 2050, we should also be focusing on preventing the blindness caused by ATT, as it is preventable and also reversible if timely identified. Hence generating information, education, and communication (IEC) materials in all DOTS clinic and educating the DOTS providers and patients about this potentially blinding complication of ATT could save the vision of hundreds of unfortunate patients losing their eyesight.

CONCLUSION

Although the incidence of ATT induced optic neuropathies was low in our study, this entity needs to be recognized early as these are potentially reversible after stopping the drug in the early stages.

LIMITATIONS

We had a limited follow up of 6 months. Longer follow up duration would have more chance of identifying ethambutol induced optic neuropathy, as it is dose and duration related. Another limitation is that we had fewer patients taking ethambutol for more than 2 months. Future studies targeting patients taking ethambutol for longer duration like severe extrapulmonary TB or DR-TB may be helpful to understand the true burden of this problem in these high-risk cases.

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ABBREVIATIONS

ATT	Anti-tubercular Treatment
BCVA	Best Corrected Visual Acuity
BE	Both Eyes
BPKLCOS	Bisheshwor Prasad Koirala Lions Centre for Ophthalmic Studies
DOTS	Directly Observed Treatment Short course
DR-TB	Drug Resistant Tuberculosis
EMB	Ethambutol
EON	Ethambutol induced Optic Neuropathy
GVF	Goldmann Visual Field
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
INH	Isoniazid
LE	Left Eye
NPL	No Perception of Light
OCT	Optical Coherence Tomography
OPD	Out Patient Department
RNFL	Retinal Nerve Fibre Layer
SD-OCT	Spectral Domain Optical Coherence Tomography
TB	Tuberculosis
TUTH	Tribhuvan University Teaching Hospital
VEP	Visual Evoked Potential
WHO	World Health Organization

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