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Incidence and Clinical Characteristics of Ethambutol-Induced Optic Neuropathy Among Tuberculosis Patients Receiving Directly Observed Treatment: A Prospective Cohort Study

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ABSTRACT

Background: Ethambutol, a first-line anti-tubercular drug, is associated with ethambutol-induced optic neuropathy (EON), a potentially irreversible toxic mitochondrial optic neuropathy. The incidence and clinical characteristics of EON differ among populations, yet prospective data from Pakistan remain limited.

Objective: To determine the incidence and clinical characteristics of ethambutol-induced optic neuropathy in tuberculosis patients undergoing directly observed treatment, using serial ophthalmological assessments.

Methodology: This prospective observational cohort study was conducted at Liaquat University Hospital, Hyderabad, Pakistan, from January 2023 to December 2024. A total of 480 tuberculosis patients initiating ethambutol-containing therapy under DOTS were enrolled. Baseline ophthalmological assessments included best-corrected visual acuity, color vision testing, visual field examination, optic disc evaluation, and optical coherence tomography (OCT).

Results: Among 452 participants who completed follow-up, 9 developed EON, corresponding to an incidence of 1.99% (95% CI: 0.92%–3.76%). The mean time to symptom onset was 4.2 ± 1.6 months. All cases were bilateral. Color vision abnormalities occurred in 77.8% of cases, and visual field defects in 88.9%. OCT demonstrated significant increases in average, temporal, and nasal retinal nerve fiber layer thickness ($p < 0.05$). Diabetes mellitus (OR: 3.42; $p = 0.014$) and renal impairment (OR: 4.86; $p = 0.008$) were identified as independent risk factors.

Conclusion: EON developed in approximately 2% of tuberculosis patients receiving ethambutol under DOTS. Diabetes mellitus and renal impairment were independent risk factors. Systematic ophthalmological monitoring, especially for high-risk patients, is essential for early detection and prevention of irreversible visual loss.

Keywords: EON; DOTS; Tuberculosis; Ophthalmological Monitoring; Pakistan

Introduction

Tuberculosis (TB) continues to pose a major global public health challenge, with approximately 10.6 million new cases and 1.3 million deaths reported each year. The World Health Organization (WHO) declared TB a global emergency in 1993, prompting the adoption of the Directly Observed Treatment, Short-course (DOTS) strategy, which has become the foundation of TB control programs worldwide.¹ This strategy promotes patient adherence by requiring direct observation of medication intake, implementing standardized treatment regimens, and systematically monitoring treatment outcomes.

Ethambutol, a first-line bacteriostatic anti-tubercular agent, has been a key component of standard anti-TB regimens since its introduction in 1962.² It is commonly administered at 15–20 mg/kg/day during the intensive phase of treatment and is available as fixed-dose combination tablets and as a single-agent formulation. Although ethambutol is generally well-tolerated, its most serious adverse effect is ethambutol-induced optic neuropathy (EON). This toxic mitochondrial optic neuropathy may cause permanent visual impairment if not identified early.^{3,4} The ocular toxicity of ethambutol was initially described by Carr and Henkind in 1962, and EON is now recognized as one of the most prevalent drug-induced optic neuropathies worldwide.²

The pathogenesis of EON is attributed to the chelating properties of ethambutol, which disrupt mitochondrial oxidative phosphorylation. This disruption results in calcium influx into mitochondria, inhibition of the electron transport chain, and depletion of adenosine triphosphate.^{3,5} These effects predominantly impact the unmyelinated, narrow-caliber fibers of the papillomacular bundle, which are rich in mitochondria and essential for central vision.³ As a result, patients commonly present with bilateral, painless, subacute visual deterioration, frequently accompanied by dyschromatopsia (particularly red-green deficiency), central or centrocecal scotomas, and temporal optic disc pallor in chronic stages.^{3,6}

The reported incidence of EON varies significantly across studies, with estimates ranging from 0.28% to over 3%, depending on study population, dosing regimens, and diagnostic criteria.^{7,8} A recent systematic review and meta-analysis identified a pooled incidence of 1.54% (95% CI: 0.81–2.49%) among patients treated with ethambutol. This variability is partially explained by differences in ethambutol dosing, treatment duration, patient demographics, and comorbid conditions that increase susceptibility to toxicity. Established risk factors include renal impairment, advanced age, low body weight, diabetes mellitus, hypertension, and smoking.⁷⁻⁹ Early detection of ethambutol-induced optic neuropathy (EON) at a potentially reversible stage remains a significant clinical challenge. Several international

guidelines recommend baseline and periodic ophthalmological assessments; however, the optimal monitoring strategy and diagnostic modalities have not been fully established.^{10,11} Optical coherence tomography (OCT) has become a valuable tool for identifying subclinical changes in the retinal nerve fiber layer (RNFL), with evidence indicating that alterations in RNFL thickness may precede the onset of clinical visual symptoms.^{12,13} The temporal quadrant of the RNFL is particularly susceptible, which corresponds to the known vulnerability of the papillomacular bundle to ethambutol toxicity.¹²

Although EON is recognized as an important complication, prospective data from Pakistan on its incidence and clinical characteristics among tuberculosis patients receiving ethambutol under the Directly Observed Treatment, Short-course (DOTS) strategy are limited. Most existing evidence is derived from retrospective studies. It is generalized to East Asian populations, but may not be generalizable to the Pakistani context because of differences in nutritional status, body weight distribution, and comorbidity profiles. Additionally, the adoption of revised national tuberculosis treatment guidelines with standardized daily dosing may have modified the risk profile for EON in recent years.

Accordingly, this prospective cohort study was conducted to determine the incidence and clinical characteristics of ethambutol-induced optic neuropathy among tuberculosis patients receiving directly observed treatment at a tertiary care hospital in Pakistan. Serial ophthalmological assessments, including visual acuity testing, color vision evaluation, visual field examination, and OCT imaging, were performed to characterize the spectrum of ocular toxicity associated with ethambutol and to identify potential risk factors that may inform clinical monitoring strategies. The findings are anticipated to support the development of evidence-based screening protocols for early detection and prevention of irreversible visual loss in tuberculosis patients receiving ethambutol-containing regimens.

Objective

To determine the incidence and clinical characteristics of ethambutol-induced optic neuropathy in tuberculosis patients undergoing directly observed treatment, using serial ophthalmological assessments.

Methodology

A prospective observational cohort study was undertaken at Liaquat University Hospital in Hyderabad, Pakistan, to assess the incidence and clinical characteristics of ethambutol-induced optic neuropathy among tuberculosis patients receiving directly observed treatment. Data collection occurred over a two-year period, from January 2023 to December 2024. The study population

included patients diagnosed with tuberculosis who were prescribed an ethambutol-containing anti-tuberculosis regimen under the directly observed treatment strategy (DOTS) at Liaquat University Hospital. Eligible participants were enrolled at the initiation of ethambutol therapy and monitored prospectively for the duration of ethambutol exposure.

The sample size was determined using the single-population proportion formula, referencing an incidence of ethambutol-induced optic neuropathy of approximately 0.28% as reported in a previous study. With an expected incidence of 0.28%, a 95% confidence level, and an absolute precision of 0.5%, the minimum required sample size was calculated to be 430 patients. Accounting for a 10% anticipated loss to follow-up, the final sample size was adjusted to 478 and rounded to 480 participants. Consecutive eligible patients were recruited until the target sample size was reached.⁸

Patients were eligible if they had a confirmed or clinically diagnosed tuberculosis infection, were prescribed ethambutol as part of their anti-tuberculosis treatment, and were willing to participate in the study. Participants were required to undergo baseline and subsequent ophthalmological assessments and provide written informed consent. Exclusion criteria included optic neuropathy, severe vision loss, significant ocular disease such as advanced glaucoma or severe retinal disease, prior long-term ethambutol use without a baseline ophthalmic examination, and inability to provide consent or complete follow-up.

Participants meeting eligibility criteria were enrolled prior to or at the initiation of ethambutol therapy. Data collection utilized a structured, pretested proforma. Baseline demographic variables included age and sex, while clinical variables encompassed tuberculosis type and site, history of previous tuberculosis treatment, relevant comorbidities, and concomitant medications. Special consideration was given to diabetes mellitus and renal impairment due to their potential impact on ocular health and ethambutol toxicity.

Recorded ethambutol treatment details included daily dose, body weight, dose in mg/kg/day, planned treatment duration, treatment regimen, and any subsequent modifications to dose or duration. Renal function was documented at baseline and during follow-up in accordance with routine clinical practice.

A baseline ophthalmological examination was conducted prior to or at the initiation of ethambutol therapy. This assessment comprised best-corrected visual acuity for each eye, color vision testing, and optic disc examination. Visual field testing was performed when feasible. Optical coherence tomography (OCT), including evaluation of the retinal nerve fiber layer (RNFL) and/or ganglion cell layer, was conducted where available. The baseline examination established ocular status before significant ethambutol exposure and served as a reference for subsequent assessments.

Participants were followed prospectively throughout the course of ethambutol treatment. Ophthalmological assessments were conducted at baseline, at 1 month, at 3 months, and subsequently every 3 months until ethambutol was discontinued. Additional assessments were performed if visual symptoms developed.

At each follow-up visit, visual acuity and color vision were assessed, and participants were specifically queried regarding visual symptoms, including blurred vision, difficulty distinguishing colors, central vision changes, or visual field disturbances. Optic disc examination was repeated, while visual field testing and OCT were performed according to the predefined schedule or when clinically indicated.

The primary outcome was the development of ethambutol-induced optic neuropathy (EON) during follow-up. EON was defined as a new deterioration in visual function during ethambutol exposure that was clinically compatible with ethambutol-related optic nerve toxicity and not attributable to other ocular or neurological conditions.

Evidence supporting a diagnosis of EON included new reductions in visual acuity, impairment of color vision, visual field abnormalities, optic disc changes, and/or compatible OCT findings. The date of ocular toxicity detection was recorded to determine the duration of ethambutol exposure prior to abnormality onset. Incidence was calculated as the number of participants who developed EON divided by the total number of participants enrolled and exposed to ethambutol, expressed as a percentage. Clinical characteristics of affected participants, including age, sex, comorbidities, ethambutol dose, dose in mg/kg/day, treatment duration, and ophthalmological findings, were documented.

Participants who developed visual symptoms or objective ophthalmological abnormalities suggestive of ethambutol toxicity underwent comprehensive ophthalmological evaluation. The treating physician and ophthalmologist determined further management, including modifying or discontinuing ethambutol when clinically indicated. The study documented any changes in anti-tuberculosis treatment and subsequent ocular findings during follow-up.

Statistical analyses were performed using SPSS version 26. The incidence of EON was determined as the percentage of exposed patients, with corresponding 95% confidence intervals. Continuous variables were summarized as mean and standard deviation or as median with interquartile range, while categorical variables were reported as frequencies and percentages. The Shapiro-Wilk test assessed normality. For between-group comparisons, either the independent samples t-test or the Mann-Whitney U test was applied, as appropriate. Within-participant changes in visual acuity, color vision, visual field parameters, and optical coherence tomography (OCT) measurements were evaluated using the paired t-test or the Wilcoxon signed-

rank test, depending on data distribution. Categorical variables, including sex, comorbidities, smoking status, dose, and duration, were compared using the chi-square test or Fisher's exact test. Risk factors for EON were identified through univariate and multivariate logistic regression analyses, adjusting for potential confounders such as age, sex, body weight, and ethambutol dose. The Kaplan-Meier method estimated the cumulative probability of EON over time. Statistical significance was set at $p < 0.05$.

The Ethics Committee of Liaquat University Hospital approved the study (Ref. 55/03-23/-). Written informed consent was obtained from all participants. Confidentiality was ensured by assigning unique study identification numbers instead of personal identifiers in the research database. Clinically significant ocular

abnormalities identified during the study were reported to the treating team for appropriate clinical management.

Results

A total of 480 patients with tuberculosis receiving ethambutol-containing anti-tuberculosis treatment under the DOTS strategy were enrolled in the study. Of these, 452 patients (94.2%) completed the planned follow-up assessments and were included in the final analysis. The remaining 28 patients (5.8%) were lost to follow-up, 12 due to transfer to other treatment centers, 8 due to refusal to continue participation, 5 due to migration to another city, and 3 due to death from causes unrelated to ocular toxicity. The mean age of participants was 43.6 ± 12.8 years (range: 18–72 years). The majority were male (268,

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants (n=452)

Characteristic	Value
Age (years), mean $\pm$ SD	43.6 $\pm$ 12.8
Age range (years)	18–72
Male, n (%)	268 (59.3)
Female, n (%)	184 (40.7)
Body weight (kg), mean $\pm$ SD	54.2 $\pm$ 9.6
Type of Tuberculosis	
Pulmonary, n (%)	372 (82.3)
Extrapulmonary, n (%)	80 (17.7)
Comorbidities	
Diabetes mellitus, n (%)	68 (15.0)
Hypertension, n (%)	42 (9.3)
Renal impairment, n (%)	24 (5.3)
Smoking history, n (%)	86 (19.0)
Ethambutol Treatment	
Daily dose (mg), mean $\pm$ SD	812.4 $\pm$ 126.8
Dose (mg/kg/day), mean $\pm$ SD	15.2 $\pm$ 2.4
Planned duration (months), mean $\pm$ SD	6.8 $\pm$ 1.4

Table 2. Distribution of Ethambutol Dose and Duration (n=452)

Parameter	Frequency (%)
Dose (mg/kg/day)	
12–15	98 (21.7)
15–20	318 (70.4)
>20	36 (8.0)
Duration of treatment (months)	
≤4	86 (19.0)
5–6	244 (54.0)
7–9	98 (21.7)
>9	24 (5.3)

59.3%), while 184 (40.7%) were female. The mean body weight was 54.2 ± 9.6 kg. Pulmonary tuberculosis was diagnosed in 372 participants (82.3%), and 80 (17.7%) had extrapulmonary tuberculosis. Diabetes mellitus was present in 68 participants (15.0%), and renal impairment, defined as serum creatinine greater than 1.5 mg/dL, was documented in 24 (5.3%). A history of smoking was reported by 86 participants (19.0%), and 42 (9.3%) had hypertension (Table 1).

The mean daily dose of ethambutol was 812.4 ± 126.8 mg, corresponding to a mean dose of 15.2 ± 2.4 mg/kg/day. Most participants (318; 70.4%) received ethambutol at a dose of 15–20 mg/kg/day. Additionally, 98 participants (21.7%) received 12–15 mg/kg/day, and 36 participants (8.0%) received more than 20 mg/kg/day. The mean duration of ethambutol exposure was 6.8 ± 1.4 months, with a range of 2 to 12 months (Table 2).

During follow-up, nine participants developed ethambutol-induced optic neuropathy (EON), resulting in an overall incidence of 1.99% (95% CI: 0.92%–3.76%) among the 452 participants who completed follow-up. For all 480 enrolled participants, the incidence was 1.88% (95% CI: 0.87%–3.55%). The mean duration of ethambutol exposure before the onset of visual symptoms was 4.2 ± 1.6 months (range: 1.5–7 months). All EON cases were bilateral; however, the severity and timing of presentation were asymmetric in four participants (44.4%). The incidence density rate was 2.94 per 1000 person-months of ethambutol exposure (Table 3).

Participants who developed EON were older (mean age 51.3 vs 43.2 years, $p=0.028$) and had lower body weight (48.6 kg vs 54.4 kg, $p=0.041$) than those without EON. Diabetes mellitus (33.3% vs 14.7%, $p=0.045$) and renal

impairment (22.2% vs 5.0%, $p=0.032$) were more common among EON cases. Ethambutol dose did not differ significantly, but symptom onset occurred after a mean of 4.2 months (Table 4).

All 9 participants with EON presented with bilateral visual acuity reduction. At the time of diagnosis, best-corrected visual acuity (BCVA) in the right eye ranged from 6/18 to 6/60 (mean logMAR: 0.68 ± 0.24), and in the left eye from 6/12 to 6/60 (mean logMAR: 0.62 ± 0.28). The mean reduction in BCVA from baseline was 0.42 ± 0.18 logMAR in the right eye and 0.38 ± 0.21 logMAR in the left eye (Table 5).

Color vision assessment using Ishihara pseudoisochromatic plates revealed abnormalities in 7 of 9 participants with EON (77.8%). Red-green deficiency was the most common, present in 4 participants (44.4%), followed by blue-yellow deficiency in 2 participants (22.2%), and combined red-green and blue-yellow deficiency in 1 participant (11.1%). Two participants (22.2%) demonstrated normal color vision at the time of EON diagnosis. All detected color vision abnormalities were bilateral.

Visual field testing was conducted in all 9 EON participants at diagnosis. Abnormal visual fields were identified in 8 participants (88.9%). The most frequent defect was central or centrocecal scotoma, observed in 4 participants (44.4%), followed by bitemporal hemianopia in 2 participants (22.2%), generalized depression in 1 participant (11.1%), and paracentral scotoma in 1 participant (11.1%). One participant (11.1%) exhibited a normal visual field despite reduced visual acuity and color vision abnormalities. Optic disc examination at diagnosis showed hyperemic disc swelling in 4 participants

Table 3. Cumulative Incidence of Ethambutol-Induced Optic Neuropathy During Follow-up

Follow-up Interval	New EON Cases (n)	Cumulative EON Cases (n)	Cumulative Incidence (%)
Baseline to 1 month	0	0	0.00
1–3 months	3	3	0.66
3–6 months	5	8	1.77
6–9 months	1	9	1.99
>9 months	0	9	1.99

(44.4%), temporal disc pallor in 3 participants (33.3%), and normal disc appearance in 2 participants (22.2%). Of the 3 participants with temporal disc pallor, 2 had a longer symptom duration before diagnosis (mean: 8.2 weeks).

Optical coherence tomography (OCT) was performed for all nine patients with EON at the time of diagnosis. Average retinal nerve fiber layer (RNFL) thickness increased to 112.4 μ m in the right eye and 114.8 μ m in the left eye compared with baseline measurements. Both temporal and nasal RNFL thicknesses were significantly higher than baseline values. Central macular thickness did not change significantly (Table 6).

All nine participants diagnosed with ethambutol-induced optic neuropathy (EON) were referred to both the treating physician and an ophthalmologist for further management. Ethambutol therapy was discontinued in all cases. The mean interval from symptom onset to cessation of ethambutol was 3.2 ± 1.4 weeks. Alternative anti-tuberculosis medications were initiated in accordance with national treatment guidelines. At the three-month follow-up after discontinuation of ethambutol, 3 participants (33.3%) had butol, partial visual recovery, defined as an improvement of at least 10% in three participants (33.3%). Four participants (44.4%) exhibited no significant improvement, and two participants (22.2%) experienced further deterioration. At six months, four participants (44.4%) demonstrated partial visual recovery, three (33.3%) remained stable, and two (22.2%) continued to have severe visual impairment. No participant achieved complete visual recovery. Color vision abnormalities persisted in all seven affected participants at the six-month follow-up. The mean final best-corrected visual acuity (BCVA) at six months after ethambutol discontinuation was 0.48 ± 0.22 logMAR in the right eye and 0.44 ± 0.26 logMAR in the left eye.

Univariate analysis identified older age ($p=0.028$), lower body weight ($p=0.041$), diabetes mellitus ($p=0.045$), and renal impairment ($p=0.032$) as significant factors associated with EON development. Multivariate logistic regression demonstrated that diabetes mellitus (OR: 3.42, 95% CI: 1.28–9.14; $p=0.014$) and renal impairment (OR: 4.86, 95% CI: 1.52–15.52; $p=0.008$) were independent

risk factors for EON after adjustment for age, sex, body weight, and ethambutol dose (Table 7).

Although the mean ethambutol dose did not differ significantly between EON and non-EON participants, a higher incidence of EON was associated with increasing dose. For participants receiving 12–15 mg/kg/day, the incidence of EON was 1.02% (1/98); for those receiving 15–20 mg/kg/day, the incidence was 1.89% (6/318); and for those receiving more than 20 mg/kg/day, the incidence was 5.56% (2/36). The difference across dose categories approached statistical significance ($p=0.052$). EON incidence increased with longer durations of ethambutol exposure. Among participants treated for four months or less, the incidence was 1.16% (1/86); for five to six months, 1.64% (4/244); for seven to nine months, 3.06% (3/98); and for more than nine months, 4.17% (1/24). This trend was statistically significant ($p=0.038$).

The mean interval from ethambutol initiation to the onset of visual symptoms was 4.2 ± 1.6 months. Kaplan-Meier analysis estimated the cumulative probability of developing EON at six months as 1.77% (95% CI: 0.72%–3.82%) and at nine months as 2.21% (95% CI: 1.02%–4.48%).

Discussion

This prospective cohort study presents current data on the incidence and clinical characteristics of ethambutol-induced optic neuropathy among tuberculosis patients undergoing directly observed treatment in Pakistan. The observed incidence of EON was 1.99% among participants who completed follow-up, aligning with the range reported in existing literature and closely matching the pooled estimate of 1.54% from a recent meta-analysis.⁷ In contrast, this finding diverges from certain earlier studies, likely due to variations in study design, population characteristics, and diagnostic criteria.

Reported incidence rates of EON in the literature range from 0.28% to 6%.^{8,14,15} For example, a retrospective study from India found an incidence of 0.28% among 1,676 patients treated with ethambutol.⁸ In contrast, a prospective Indian study documented a 6% incidence

among 50 patients, with all affected individuals aged above 65 years.¹⁵ Variability in these findings may result from differences in study design, sample size, follow-up duration, dosing regimens, and the sensitivity of diagnostic methods.

The incidence observed in the present study (1.99%) is higher than the 0.28% reported by Singh et al. from Central India.⁸ This difference may be attributed to the prospective design of the current study, which included systematic serial ophthalmological assessments at predefined intervals, including OCT imaging. Retrospective studies often rely on medical records and may underestimate the true incidence of EON, as cases of subclinical or mild toxicity may go undetected if patients do not seek ophthalmological consultation. Additionally, the comprehensive baseline and follow-up assessments in this study, including color vision testing, visual field examination, and OCT, are more sensitive for detecting early or subclinical toxicity than routine clinical examination.

In contrast, the incidence in this study is lower than the 6% reported by a prospective Indian study.¹⁵ This discrepancy may be due to differences in patient demographics and dosing regimens. In the referenced study, all affected patients were above 65 years of age, and the mean age of the cohort was likely higher than in the present study (43.6 years). Advanced age is a recognized risk factor for EON, likely due to age-related decline in renal function and reduced ethambutol clearance.^{3,9} Furthermore, the study by Sharma et al. included frequent monthly assessments, which may have

identified milder cases that would not be detected with less intensive monitoring.¹⁵

The incidence in our study is also comparable to the 1.88% reported among patients with ophthalmology encounters in a Thai⁹ retrospective study and the 1.29% reported from Taiwan.¹⁶ These similarities suggest that the incidence of EON in our Pakistani cohort is consistent with the broader Asian experience, despite differences in healthcare infrastructure and TB treatment delivery.

The present study identified older age, lower body weight, diabetes mellitus, and renal impairment as significant factors associated with the development of EON.^{7,9,17}

Multivariate analysis demonstrated that diabetes mellitus (OR: 3.42) and renal impairment (OR: 4.86) were independent risk factors. These results align with previous research that has recognized renal dysfunction as a primary risk factor for EON. Ethambutol is predominantly excreted unchanged by the kidneys; thus, renal impairment results in drug accumulation and prolonged exposure, increasing the risk of toxicity.^{3,9}

Several studies have implicated diabetes mellitus as a risk factor for EON, although the evidence remains inconsistent.^{3,18} The proposed mechanism involves diabetes-induced microvascular changes and impaired mitochondrial function, which may enhance ethambutol's toxic effects on the optic nerve.¹⁸ The observed significant association between diabetes and EON in this study (33.3% of EON cases versus 14.7% of non-EON cases) is consistent with some previous reports.¹⁸ However, this finding contrasts with the Thai study by Chaitanuwong et al., which did not identify a significant association

Table 4. Comparison of Clinical Characteristics Between EON and Non-EON Participants

Characteristic	EON (n=9)	Non-EON (n=443)	p-value
Age (years), mean $\pm$ SD	51.3 $\pm$ 10.7	43.2 $\pm$ 12.6	0.028*
Male, n (%)	6 (66.7)	262 (59.1)	0.65
Body weight (kg), mean $\pm$ SD	48.6 $\pm$ 7.2	54.4 $\pm$ 9.5	0.041*
Diabetes mellitus, n (%)	3 (33.3)	65 (14.7)	0.045*
Hypertension, n (%)	2 (22.2)	40 (9.0)	0.19
Renal impairment, n (%)	2 (22.2)	22 (5.0)	0.032*
Smoking history, n (%)	3 (33.3)	83 (18.8)	0.29
Ethambutol dose (mg/kg/day), mean $\pm$ SD	14.8 $\pm$ 2.1	15.2 $\pm$ 2.4	0.62
Treatment duration (months), mean $\pm$ SD	4.2 $\pm$ 1.6	6.9 $\pm$ 1.3	<0.001*

*Statistically significant (p<0.05)

Table 5. Visual Acuity at Baseline and at EON Diagnosis (n=9)

Visual Acuity	Right Eye (n=9)		Left Eye (n=9)	
	Baseline	EON Diagnosis	Baseline	EON Diagnosis
6/6–6/9, n (%)	9 (100)	0 (0)	9 (100)	1 (11.1)
6/12–6/18, n (%)	0 (0)	3 (33.3)	0 (0)	3 (33.3)
6/24–6/36, n (%)	0 (0)	4 (44.4)	0 (0)	3 (33.3)
6/60 or worse, n (%)	0 (0)	2 (22.2)	0 (0)	2 (22.2)

between diabetes and EON.⁹ This discrepancy may be attributable to differences in diabetes control, disease duration, and the presence of diabetic retinopathy, factors not systematically assessed in the present study.

The observed association between lower body weight and EON is clinically plausible, as individuals with lower body weight receive a higher weight-adjusted dose of ethambutol for a given daily dose. Previous studies have also identified low body weight and malnutrition as risk factors for EON.^{3,17} This finding highlights the necessity of weight-based dosing and vigilant monitoring in underweight patients, particularly in TB-endemic regions. In contrast to some previous studies, the present analysis did not identify statistically significant associations between hypertension, smoking, or HIV co-infection and EON.^{9,17} The relatively small number of EON cases may have limited the statistical power to detect modest associations. The Thai study reported hypertension and smoking as significant risk factors in unadjusted analysis, with smoking remaining significant in adjusted analysis (OR: 7.06).⁹ The absence of association in this cohort may be explained by the comparatively low prevalence of smoking (19.0%) and hypertension (9.3%) relative to other populations.

The clinical presentation of EON observed in this cohort aligns with the classical features of ethambutol toxicity. All affected participants had a gradual reduction in visual acuity, with most demonstrating color vision abnormalities (77.8%) and visual field defects (88.9%). The mean interval from ethambutol initiation to symptom onset was 4.2 months, consistent with the reported range of 2–8 months in the literature.^{3,9} The predominance of red-green color deficiency (44.4%) corresponds with the established susceptibility of the papillomacular bundle, which contains colour-sensitive ganglion cells, to ethambutol toxicity.¹⁵

Visual field findings in this study were heterogeneous, with central or centrocecal scotomas being the most prevalent (44.4%), followed by bitemporal hemianopia (22.2%). These results are consistent with existing literature, which describes both central and peripheral

visual field defects in EON.^{3,19} The occurrence of bitemporal hemianopia in two participants is noteworthy, as this pattern suggests optic chiasm involvement, a manifestation reported in ethambutol toxicity but less common than retrobulbar neuritis.¹⁹

Optical coherence tomography (OCT) findings demonstrated significant increases in average, temporal, and nasal retinal nerve fiber layer (RNFL) thickness at the time of EON diagnosis compared to baseline. These results align with the early phase of EON, characterized by axonal swelling resulting from mitochondrial dysfunction and impaired axonal transport prior to subsequent axonal loss and thinning.^{12,20} The temporal quadrant exhibited the most pronounced increase, consistent with the established vulnerability of the papillomacular bundle to ethambutol toxicity.¹²

Previous studies have reported both increases and decreases in RNFL thickness in EON, depending on the timing of assessment relative to symptom onset.^{12,20} The temporal evolution of RNFL changes highlights the importance of serial OCT assessments and the necessity of interpreting OCT findings within the context of disease duration.

Notably, the observed increase in RNFL thickness in the temporal and nasal quadrants contrasts with the findings of Singh et al., who reported significant associations between longer treatment duration and increased left temporal RNFL thickness.⁸ These differences may be attributable to the timing of OCT assessment relative to symptom onset and the duration of ethambutol exposure prior to discontinuation.

Visual outcomes in this cohort were minimal: only 44.4% of affected patients showed partial visual recovery at 6 months after ethambutol discontinuation, and no patients achieved complete recovery. These findings align with the increasing recognition that ethambutol optic neuropathy (EON) is not always fully reversible, contrary to earlier assumptions.³ The comparatively lower recovery rate may be explained by delays in diagnosis and discontinuation of ethambutol, as the mean interval from symptom onset to drug cessation was 3.2 weeks. Previous studies have

Table 6. OCT Findings in EON Participants (n=9)

Parameter	Right Eye		Left Eye		p-value (Right)	p-value (Left)
	Baseline	EON	Baseline	EON		
Average RNFL (μm)	98.6 ± 9.8	112.4 ± 14.6	99.2 ± 10.4	114.8 ± 15.2	0.018*	0.012*
Temporal RNFL (μm)	72.6 ± 8.4	82.4 ± 11.2	71.8 ± 7.9	84.1 ± 12.6	0.008*	0.006*
Nasal RNFL (μm)	84.2 ± 10.8	108.6 ± 13.4	83.6 ± 11.2	110.2 ± 14.8	0.021*	0.017*
Superior RNFL (μm)	106.8 ± 12.4	108.2 ± 13.6	107.2 ± 11.8	109.4 ± 14.2	0.58	0.52
Inferior RNFL (μm)	114.6 ± 13.2	116.2 ± 14.8	115.2 ± 12.6	117.4 ± 15.4	0.62	0.56
Central subfield macular thickness (μm)	312.6 ± 18.4	298.4 ± 22.6	310.8 ± 19.6	296.8 ± 24.2	0.12	0.15

*Statistically significant (p<0.05)

demonstrated that earlier discontinuation of ethambutol is associated with improved visual outcomes.^{7,15}

The persistence of color vision abnormalities in all affected participants at 6 months is noteworthy and consistent with existing literature, which suggests that dyschromatopsia may be more resistant to recovery than visual acuity.¹⁵ The observation of temporal disc pallor in three participants at presentation, an indicator of chronic axonal loss, may be associated with a poorer prognosis, as indicated by Chen et al.¹⁶

Although the mean ethambutol dose did not differ significantly between EON and non-EON participants, a trend toward higher incidence was observed with increasing dose categories (1.02% at 12–15 mg/kg/day, 1.89% at 15–20 mg/kg/day, and 5.56% at greater than 20 mg/kg/day). This dose-dependent trend is consistent with the established relationship between ethambutol dose and risk of toxicity.³ Notably, EON occurred even at doses traditionally considered "safe" (12–15 mg/kg/day), reinforcing the concept that no ethambutol dose is entirely without risk.⁸ Recent evidence has documented toxicity at doses as low as 12.3 mg/kg/day.⁸

A significant trend toward higher incidence was also observed with longer treatment duration, consistent with the cumulative dose effect of ethambutol.^{7,9} The mean duration of ethambutol exposure before symptom onset in this study (4.2 months) was shorter than the mean treatment duration reported in some other studies, which may reflect the impact of an intensive monitoring protocol that facilitated earlier detection.^{5,9}

Clinical Implications

Several key clinical implications emerge from this study. The observed 1.99% incidence of EON in the cohort

underscores the necessity for systematic ophthalmological monitoring in patients receiving ethambutol regimens. Diabetes mellitus and renal impairment are identified as independent risk factors, suggesting that these patients require closer surveillance and potentially more frequent assessments. Importantly, EON may develop even at standard doses and within a few months of treatment, which reinforces the need for baseline eye examinations and early patient education regarding visual symptoms.

Existing guidelines for EON monitoring vary and frequently lack clear criteria regarding assessment frequency or methods. The application of serial visual acuity, color vision, visual field testing, and optical coherence tomography (OCT) in this study demonstrates that multimodal screening enhances detection rates. However, resource constraints in high-burden tuberculosis settings may limit the feasibility of comprehensive monitoring for all patients. Consequently, risk-based screening targeting high-risk groups, such as individuals with renal impairment, diabetes, advanced age, or low body weight, represents a practical approach.

Strengths

Several strengths characterize this study. The use of a prospective cohort design with a relatively large sample size (n=480) enabled accurate estimation of incidence. Comprehensive serial ophthalmological assessments, including optical coherence tomography (OCT) imaging, facilitated early detection of subclinical toxicity. Conducting the study in a real-world DOTS setting increases generalizability to high-burden tuberculosis regions. Rigorous statistical methods, such as multivariate regression and Kaplan-Meier analysis, enhanced

Table 7. Multivariate Logistic Regression Analysis of Risk Factors for EON

Variable	Adjusted OR	95% CI	p-value
Age (per year increase)	1.04	0.98–1.10	0.21
Male sex	1.32	0.42–4.18	0.64
Body weight (per kg increase)	0.94	0.86–1.02	0.15
Diabetes mellitus	3.42	1.28–9.14	0.014*
Renal impairment	4.86	1.52–15.52	0.008*
Ethambutol dose (per mg/kg/day increase)	1.08	0.82–1.42	0.58

*Statistically significant ($p < 0.05$)

the identification of risk factors.

Limitations

Several limitations should be considered. First, the sample included only 9 EON cases, which reduced the statistical power for risk factor analysis. Second, follow-up was limited to the duration of ethambutol treatment and 6 months thereafter; longer-term outcomes were not assessed. Third, electrophysiological tests such as visual evoked potentials, which may detect toxicity earlier than OCT, were not performed. Fourth, as a single-center study, the findings may not be generalizable to other settings. Fifth, nutritional status was not systematically evaluated, which could confound the association between low body weight and EON. Finally, the absence of a control group not receiving ethambutol precludes attributing all visual changes solely to the drug.

Conclusions

This prospective cohort study demonstrates that ethambutol-induced optic neuropathy affects approximately 2% of tuberculosis patients undergoing directly observed treatment in a Pakistani tertiary care setting. The neuropathy typically presents bilaterally within the initial four to five months of therapy, with color vision abnormalities and visual field defects as common manifestations. Diabetes mellitus and renal impairment were identified as independent risk factors, indicating the necessity for increased vigilance in these populations. Optical coherence tomography identified significant retinal nerve fiber layer thickening at diagnosis, reinforcing its utility for early detection. Visual recovery was frequently incomplete, even after prompt discontinuation of ethambutol, with fewer than half of affected patients experiencing partial improvement and none

achieving full recovery. These results underscore the importance of baseline and periodic ophthalmological assessments for all patients receiving ethambutol-containing regimens, especially those with diabetes or renal impairment. Early identification of visual symptoms and immediate cessation of ethambutol are essential for preserving visual function. The findings support the adoption of risk-stratified screening protocols in tuberculosis control programs and highlight the need for greater awareness among clinicians and patients regarding the risk of irreversible visual loss associated with ethambutol therapy.

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