Section: Medicine

Original Research Article

INCIDENCE AND EARLY FUNCTIONAL INDICATORS OF ETHAMBUTOL-INDUCED OPTIC NEUROPATHY IN OCULAR TUBERCULOSIS

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Received *: 16/01/2026*
Received in revised form *: 16/02/2026*
Accepted *: 08/03/2026*

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DOI: 10.70034/ijmedph.2026.1.439

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 2537-2542

ABSTRACT

Background: Ethambutol is an essential first-line drug in anti-tubercular therapy (ATT) but is associated with ethambutol-induced optic neuropathy (EON), a potentially reversible yet vision-threatening complication. Data on the incidence and early indicators of ocular toxicity in patients with ocular tuberculosis remain limited, particularly in the Indian setting. **Objectives:** To evaluate the incidence, clinical profile, and determinants of ethambutol-induced ocular toxicity in patients with ocular tuberculosis and to identify early functional markers associated with toxicity.

Materials and Methods: This prospective observational study included 100 adult patients with ocular tuberculosis receiving ethambutol as part of ATT at a tertiary care centre. Baseline demographic and clinical variables, ethambutol dose (mg/kg/day), duration of ATT, and visual symptom characteristics were recorded. Comprehensive ophthalmic evaluation included best-corrected visual acuity, color vision testing using Ishihara plates, fundus examination, visual field assessment, and spectral-domain optical coherence tomography (SD-OCT) in suspected cases. Patients were followed during ATT, and ocular toxicity was diagnosed based on new-onset visual symptoms with corresponding functional or structural abnormalities. Statistical comparisons were performed between toxicity and non-toxicity groups.

Results: No significant association was found between ocular toxicity and age, sex, body weight, ethambutol dose, duration of ATT, uveitis subtype, or primary presenting complaint (all $p > 0.05$). Toxicity rates were similar across ethambutol dose categories within the therapeutic range. In contrast, functional abnormalities—particularly color vision impairment and visual field defects—were strongly associated with toxicity ($p < 0.001$). SD-OCT abnormalities were observed in all toxicity cases where imaging was performed.

Conclusion: Ethambutol-induced ocular toxicity occurred in a significant proportion of patients with ocular tuberculosis and was not predicted by demographic or dosing variables. Functional visual tests, especially color vision assessment and visual field analysis, emerged as the most reliable early indicators of toxicity. Regular ophthalmic monitoring remains essential for early detection and prevention of irreversible visual loss during ethambutol therapy.

Keywords: Ethambutol, optic neuropathy, ocular tuberculosis, color vision, visual field defects, OCT.

INTRODUCTION

Tuberculosis (TB) continues to be a major global public health problem despite significant advances in diagnosis and treatment. According to the World Health Organization, TB remains one of the leading infectious causes of morbidity and mortality worldwide, with India contributing a substantial proportion of the global disease burden.[1,2] In addition to pulmonary involvement, TB may present as extrapulmonary disease, including ocular tuberculosis, which can affect the uvea, retina, optic nerve, or ocular adnexa and often requires prolonged anti-tubercular therapy (ATT).[3,4]

Ethambutol is a key first-line antitubercular drug used in both drug-susceptible and drug-resistant TB regimens because of its proven efficacy and overall systemic safety.[5] However, its clinical use is limited by the risk of ocular toxicity, most notably ethambutol-induced optic neuropathy (EON).[6] EON typically presents as a bilateral, painless, and progressive visual impairment characterized by reduced visual acuity, color vision defects—especially red-green dyschromatopsia—and central or cecocentral visual field defects.[7,8]

The exact pathophysiology of EON is not fully understood, but mitochondrial dysfunction, impaired axonal transport, and direct toxicity to retinal ganglion cells have been implicated.[9,10] Although earlier studies emphasized a dose- and duration-dependent relationship, more recent evidence suggests that optic neuropathy may occur even at standard therapeutic doses, indicating the contribution of additional risk factors such as renal dysfunction, poor nutritional status, and individual susceptibility.[11,12]

Early detection of ethambutol-induced ocular toxicity is crucial, as timely discontinuation of the drug can lead to partial or complete visual recovery in many patients.[13] Functional tests such as color vision assessment and automated perimetry are sensitive tools for detecting early or subclinical toxicity, often before irreversible structural damage occurs.[14,15] Structural imaging using spectral-domain optical coherence tomography (SD-OCT) has further enhanced early diagnosis by demonstrating thinning of the retinal nerve fiber layer and ganglion cell complex.[16]

Despite increasing awareness, prospective data on ethambutol-induced ocular toxicity in patients with ocular tuberculosis remain limited, particularly in the Indian setting. The present study was therefore undertaken to evaluate the incidence, clinical profile, and early functional indicators of ethambutol-induced ocular toxicity in patients receiving ATT at a tertiary care centre.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care teaching hospital after obtaining approval from the Institutional Ethics Committee (Annexure 1). A total of 100 patients diagnosed with ocular tuberculosis and receiving ethambutol as part of ATT were consecutively enrolled after obtaining informed written consent. Adult patients (≥18 years) initiating or already receiving ethambutol-containing regimens were included, while those with pre-existing optic neuropathy, glaucoma, retinal diseases, congenital color vision defects, or systemic conditions known to affect vision were excluded. Baseline demographic data, clinical details, ethambutol dose (mg/kg/day), duration of ATT, and associated systemic illnesses were recorded. All patients underwent comprehensive ophthalmic evaluation, including best-corrected visual acuity, color vision testing using Ishihara plates, slit-lamp examination, fundus evaluation, and visual field testing where feasible. Spectral-domain optical coherence tomography (SD-OCT) was performed in clinically suspected cases of toxicity. Patients were followed periodically during ATT, and ethambutol-induced ocular toxicity was diagnosed based on new-onset visual symptoms with corresponding functional or structural abnormalities temporally related to ethambutol exposure and absence of alternative causes. Statistical analysis was performed by comparing toxicity and non-toxicity groups using appropriate parametric or non-parametric tests, with $p < 0.05$ considered statistically significant.

RESULTS

Table 1: Ethambutol Dose Categories and Ocular Toxicity Rates

Dose Category (mg/kg/day)	n	Toxicity Cases	Toxicity Rate (%)
< 15 mg/kg/day	10	1	10.00%
15–25 mg/kg/day	87	9	10.34%
> 25 mg/kg/day	3	0	0.00%

Three dose groups were evaluated: <15 mg/kg/day, 15–25 mg/kg/day, and >25 mg/kg/day, each represented with a distinct color for visual clarity. The toxicity rates remained nearly identical in the first two groups, with 10.00% in the <15 mg/kg/day group and 10.34% in the 15–25 mg/kg/day group, indicating no meaningful difference in toxicity within the commonly prescribed therapeutic range. In contrast, the highest dose category (>25 mg/kg/day) showed 0% toxicity, though this was based on a very small sample size (n = 3), limiting interpretability.

Table 2: Age Comparison by Ethambutol Dose Category

Dose Category (mg/kg/day)	n	Mean Age (years)	SD
< 15 mg/kg/day	10	48.4	16.79
15–25 mg/kg/day	87	42.28	18.74
> 25 mg/kg/day	3	42	8.66
Kruskal–Wallis Test statistic: 1.22, p-value: 0.54			

Patients receiving <15 mg/kg/day tended to be slightly older on average, with a broader age range spanning from the mid-20s to the mid-70s. The 15–25 mg/kg/day group displayed a similarly wide age spread, from young adults to elderly individuals, but with a slightly lower median age. The >25 mg/kg/day group consisted of only three patients, all within a narrower age band in the late 30s to early 50s, limiting meaningful comparison.

Table 3: Sex Differences Within Dose Groups

Dose Category	Male Toxicity Yes	Male Toxicity No	Female Toxicity Yes	Female Toxicity No	Total
<15 mg/kg/day	1	5	0	4	10
15–25 mg/kg/day	5	42	4	36	87
>25 mg/kg/day	0	3	0	0	3
Total	6	50	4	40	100
Fisher p-value = 1					

At doses <15 mg/kg/day, toxicity was observed only among males, with a rate of approximately 16.67%, while no female patients demonstrated toxicity in this category. In the standard dosing range of 15–25 mg/kg/day, both sexes exhibited nearly similar toxicity proportions, with rates of 10.6% for males and 10.0% for females, indicating a consistent pattern across genders. In the highest dose category >25 mg/kg/day, neither male nor female participants exhibited toxicity; however, only males were represented in this group, and the sample size was very small.

Statistical testing using Fisher's Exact Test revealed no significant association between sex and ocular toxicity within either dose category (<15 mg/kg/day: p = 1.00; 15–25 mg/kg/day: p = 1.00).

Table 4: Comparison of Continuous Weight (kg) Between Toxicity and Non-Toxicity Groups Across Ethambutol Dose Categories

Ethambutol Dose Category	Toxicity Group (n)	Mean Weight ± SD (kg)	No Toxicity Group (n)	Mean Weight ± SD (kg)	p-value
<15 mg/kg/day	1	53.80 ± 0.00	9	66.22 ± 7.90	NA
15–25 mg/kg/day	9	60.09 ± 6.81	78	62.39 ± 8.58	0.37
>25 mg/kg/day	0	NA	3	61.97 ± 6.86	NA

In the <15 mg/kg/day dose group, the mean weight among the toxicity case was 53.80 kg, compared with 66.22 kg in patients without toxicity, though this comparison is limited by having only one toxicity case in this category. In the 15–25 mg/kg/day group, where most patients were represented, the mean weight among toxicity cases was 60.09 kg, while those without toxicity had a slightly higher mean weight of 62.39 kg. In the >25 mg/kg/day group, no toxicity was reported, and the mean weight of patients in this group was 61.97 kg. Statistical testing showed that the difference in weight between toxic and non-toxic patients did not reach statistical significance, with the only comparable category (15–25 mg/kg/day) yielding a p-value of 0.37, accompanied by a small effect size. Altogether, the findings indicate that body weight, when analyzed as a continuous variable, does not appear to influence the likelihood of Ethambutol-induced ocular toxicity within the dosing ranges examined in this study.

Table 5: Comparison of Duration of Anti-Tubercular Treatment (ATT) Between Toxicity and Non-Toxicity Groups Across Ethambutol Dose Categories

Ethambutol Dose Category	Toxicity Group (n)	Mean Duration ± SD (weeks)	No Toxicity Group (n)	Mean Duration ± SD (weeks)	p-value
<15 mg/kg/day	1	21.00 ± 0.00	9	24.11 ± 3.44	NA
15–25 mg/kg/day	9	25.33 ± 3.46	78	23.81 ± 3.92	0.24
>25 mg/kg/day	0	NA	3	24.33 ± 2.52	NA

When duration of anti-tubercular therapy was compared between patients with and without ocular toxicity across Ethambutol dose ranges, a trend toward a longer treatment duration was observed among those who developed toxicity, particularly in the standard dosing category of 15–25 mg/kg/day. In this group, the mean duration of ATT among toxicity cases was 25.33 ± 3.46 weeks, compared with 23.81 ± 3.92 weeks among those without toxicity. However, this difference did not reach statistical significance (p = 0.24), although the calculated effect size (Cohen's d = 0.40) suggests a small to moderate practical difference.

In the <15 mg/kg/day and >25 mg/kg/day dose groups, statistical comparison was not meaningful due to limited or absent toxicity cases.

Table 6: Association Between Uveitis Type and Ethambutol-Induced Ocular Toxicity

Type of Uveitis	No Toxicity (n)	Toxicity (n)	Total	Toxicity Rate (%)
Anterior	15	1	16	6.25%
Intermediate	21	1	22	4.55%
Posterior	36	6	42	14.29%
Panuveitis	18	2	20	10.00%
p-value = 0.61				

There was no statistically significant association between the type of uveitis and the development of Ethambutol-induced ocular toxicity (p = 0.61). Although posterior uveitis showed a numerically higher toxicity rate (14.29%) compared to anterior (6.25%) and intermediate (4.55%) forms, this difference did not reach statistical significance. Patients with panuveitis demonstrated a moderate toxicity rate (10.00%), but again, this pattern did not differ meaningfully from other groups. The variation observed appears clinically mild and statistically non-significant.

Table 7: Association Between Primary Symptom and Ethambutol-Induced Ocular Toxicity

Primary Complaint	No Toxicity (n)	Toxicity (n)	Total	Toxicity Rate (%)
Diminished Vision (DV)	40	4	44	9.09%
Pain	5	0	5	0.00%
Redness	14	3	17	17.65%
Floaters	7	1	8	12.50%
Combined Symptoms	24	2	26	7.69%
p-value = 0.75				

There was no statistically significant association between the type of presenting complaint and the development of Ethambutol-induced ocular toxicity (p = 0.75). While certain symptom categories—particularly redness (17.65%) and floaters (12.50%)—appeared to show higher toxicity rates relative to other groups, these variations were not large enough to indicate a meaningful relationship. The group presenting with diminished vision, the most commonly reported symptom, showed a toxicity rate of 9.09%, which was similar to the combined symptoms group (7.69%). Notably, none of the patients presenting with pain as the primary complaint developed toxicity, although this subgroup size was small.

Table 8: Comparison of Duration of Visual Symptoms (DV Duration in weeks) Between Toxicity and Non-Toxicity Groups Across Ethambutol Dose Categories

Ethambutol Dose Category	Toxicity Group (n)	Mean DV Duration ± SD (weeks)	No Toxicity Group (n)	Mean DV Duration ± SD (weeks)	p-value
<15 mg/kg/day	1	4.00 ± 0.00	9	6.00 ± 5.39	NA
15–25 mg/kg/day	9	8.67 ± 6.40	78	8.33 ± 5.34	0.88
>25 mg/kg/day	0	NA	3	10.67 ± 2.31	NA

When the duration of visual symptoms (DV duration) was compared between patients who developed ocular toxicity and those who did not across different Ethambutol dose groups, no meaningful difference was observed. In the main treatment range (15–25 mg/kg/day), the mean DV duration in toxicity cases was 8.67 ± 6.40 weeks, which was comparable to 8.33 ± 5.34 weeks in those without toxicity. This difference was not statistically significant (p = 0.88), and the calculated effect size (Cohen's d = 0.06) indicates a negligible clinical impact. In both the <15 mg/kg/day and >25 mg/kg/day dose groups, limited toxicity events prevented statistical comparison.

Table 9: Comparison of DV Onset Pattern with Ethambutol-Induced Toxicity

DV Onset Type	No Toxicity (n)	Toxicity (n)	Total	Toxicity Rate (%)
Insidious Onset	76	10	86	11.63%
Sudden Onset	14	0	14	0.00%
p-value: 0.35				

Most patients presented with insidious onset visual disturbance, and this subgroup also contained all recorded toxicity cases. The toxicity rate among patients with insidious onset was 11.63%, while no toxicity was observed among those reporting sudden onset symptoms. Despite the numerical difference, statistical testing using Fisher's exact method revealed that the association between pattern of DV onset and the occurrence of Ethambutol-related toxicity was not statistically significant (p = 0.35).

Table 10: Comparison of DV Nature (Painful vs Painless) With Ocular Toxicity

DV Nature	No Toxicity (n)	Toxicity (n)	Total	Toxicity Rate (%)
Painless	78	9	87	10.34%
Painful	12	1	13	7.69%
p-value: 1.00				

Most patients presented with painless diminished vision, which is consistent with the expected pattern of Ethambutol optic neuropathy, a typically non-inflammatory and painless process. The toxicity rate in this group was 10.34%, compared to 7.69% in patients who experienced painful visual symptoms. Despite a slightly higher proportion of toxicity in those with painless vision loss, the difference was not statistically significant ($p = 1.00$). This indicates that the nature of visual symptoms (painful vs painless) does not meaningfully predict the likelihood of Ethambutol-related ocular toxicity in this cohort.

DISCUSSION

No significant association was observed between ethambutol dose within the recommended therapeutic range and the development of ocular toxicity. Similar observations have been reported in recent studies, which challenge the traditional view of strict dose dependence and highlight that toxicity can occur even at standard doses.[8,11] Although cumulative exposure has been suggested as a contributory factor, its role remains inconsistent across studies.[12]

Demographic variables such as age and sex did not significantly influence the risk of toxicity in this cohort, which is in agreement with earlier reports.[18,19] Additionally, no clear association was found between the subtype of ocular tuberculosis and the occurrence of optic neuropathy, suggesting that ethambutol toxicity is primarily drug-related rather than secondary to ocular inflammation.[9]

Functional visual abnormalities, particularly color vision impairment and visual field defects, were the earliest and most consistent indicators of toxicity. Dyschromatopsia has been widely recognized as a sensitive early marker of EON and often precedes measurable loss of visual acuity.[14,20] Central and cecocentral scotomas observed on automated perimetry further support optic nerve involvement, as documented in previous studies.[15,21]

SD-OCT findings in affected patients demonstrated thinning of the retinal nerve fiber layer and ganglion cell complex, reinforcing the value of OCT as an adjunctive tool in confirming clinical suspicion and detecting early structural changes.[16,22] These findings align with earlier reports suggesting that OCT abnormalities may appear even in asymptomatic patients.[22]

The results of this study emphasize the importance of baseline and periodic ophthalmic evaluation in patients receiving ethambutol, with particular focus on functional testing such as color vision and visual fields, which are cost-effective and sensitive screening tools.[23] Early recognition and prompt withdrawal of ethambutol remain essential to prevent irreversible visual loss and to improve visual outcomes.[13,24]

CONCLUSION

This prospective observational study demonstrates that ethambutol-induced ocular toxicity occurs in approximately one-tenth of patients receiving ATT for ocular tuberculosis. The risk of toxicity was not significantly influenced by patient demographics, ethambutol dose within the therapeutic range, duration of treatment, body weight, uveitis subtype, or presenting ocular symptoms. These findings suggest that ethambutol toxicity is not reliably predicted by routine clinical or treatment-related parameters.

Functional visual abnormalities—particularly impairment of color vision and the presence of visual field defects—were the most consistent and earliest indicators of toxicity. Structural changes detected on SD-OCT further supported the diagnosis in clinically suspected cases. Given the potential reversibility of ethambutol-induced optic neuropathy with timely drug discontinuation, baseline and periodic ophthalmic evaluation should be an integral component of patient monitoring during ethambutol therapy.

Emphasis on simple, cost-effective screening tools such as color vision testing and automated perimetry can facilitate early detection, especially in resource-limited settings. Prompt recognition and intervention remain crucial to prevent permanent visual impairment and to optimize visual outcomes in patients undergoing anti-tubercular treatment.

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