BJHS
Birat Journal of Health Sciences

**ISSN:**

2542-2758 (Print) 2542-2804 (Online)

**ARTICAE INFO:**

Received Date:02 January, 2025
Accepted Date: 02 April, 2025
Published Date: 30 April, 2025

**KEYWORDS:**

Cecocentral scotoma, Ethambutol induced optic neuropathy, Optical coherence tomography(OCT), Tuberculosis, Visual dysfunction, Visual evoked responses.

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Access the article online

**DOI:** 10.62065/bjhs673

**CITATION:**

Sitaula S, Shah CP, Dahal H, Dahal M, Sharma AK. Visual Function In Ethambutol Induced Optic Neuropathy At a Tertiary Eye Centre: A Retrospective Study. 2025; 9 (2): 83-89.



# Visual Function In Ethambutol Induced Optic Neuropathy At a Tertiary Eye Centre: A Retrospective Study

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## ABSTRACT

Introduction: Ethambutol is an important and widely used drug in the treatment of both tubercular and non-tubercular mycobacterial disease as it is the least toxic of the first line antituberculosis drugs. The main disadvantage of this drug is its associated ocular toxicity, manifesting as optic neuropathy.

Objectives: To describe the demography, risk factors and visual function in Ethambutol induced Optic Neuropathy (EON) among patients presenting at a tertiary eye centre in Nepal

Methodology: This retrospective study was conducted at B.P. Koirala Lions Centre for Ophthalmic Studies, Institute of Medicine, where all consecutive patients with ethambutol induced optic neuropathy presenting from 1st April 2022 to 30th March 2024 were recorded. Parameters recorded were patient demographics (age, gender and ethnicity), presenting complaints, duration and dosages of ethambutol, body weight, visual acuity, colour vision, contrast sensitivity and visual field.

Results: There were 14 patients (28 eyes) of ethambutol induced optic neuropathy. The mean age of patients taking ethambutol was 50.64± 15.8 years with mean daily dose of 18.27 ± 2.29 mg/kg per day. Bilateral ocular involvement was seen with visual acuity ranging from CFCF to 20/60 in one or both eyes. The most common color vision defect was nonspecific defect seen in six patients. The most common visual field defect was centrocecal scotoma in six cases. Mean contrast sensitivity was 1.50±0.32 log units. Thinning of the RNFL and GCC were seen in all cases of EON and the thinning correlated with the severity of visual loss.

Conclusions: EON was seen at a mean dose of 18.27mg/kg and mean duration of 7.25 months with moderate to severe visual loss and decrease in contrast sensitivity and visual field defects. Average RNFL thinning and GCC thinning correlated with the severity of visual loss seen in EON subjects. Awareness and early diagnosis can help reduce the unnecessary blindness due to this condition in the susceptible group.

## INTRODUCTION

Ethambutol is an important bacteriostatic antimicrobial drug widely used in the treatment of both tubercular and non-tubercular mycobacterial disease. The main disadvantage of this drug is its associated ocular toxicity, manifesting as optic neuropathy. Ethambutol has been used as part of the treatment protocol for tuberculosis since the 1960's.[1] A dose-related optic neuropathy was recognized affecting 1.5% of patients in one series of 800 patients.[2] Ethambutol chelates zinc,

which is an important factor in nerve function in general, and in the optic nerve function in particular.[3]

Visual loss in ethambutol optic neuropathy can present as central or peripheral field loss with or without color vision defects.4 Typically, at a dose of under 15 mg/kg per day, optic neuropathy is unlikely to develop, but at doses of 15-25 mg/kg per day, visual symptoms may develop over a period of months.[5-7] Fortunately, some visual improvement may occur with discontinuation of the drug, though some visual field and contrast sensitivity abnormalities may persist.6 Various studies have used visual acuity, visual field test, retinal nerve fiber layer(RNFL) thickness, color vision test, contrast sensitivity test, and electrophysiology like visual evoked potential (VEP) as diagnostic tools to evaluate ethambutol induced optic neuropathy (EON). Changes in RNFL thickness and VEP occur even earlier than clinical symptoms and can be used to diagnose subclinical EON.[8-9]

This study was performed to describe the demographic characteristics of patients with EON, dose and duration of ethambutol use and visual dysfunction including visual acuity, color vision dysfunction, changes in contrast sensitivity, visual field defects and changes in OCT parameters(RNFL and GCC) and visual evoked responses in Ethambutol induced Optic Neuropathy(EON) patients presenting at a tertiary eye centre in Nepal.

## METHODOLOGY

This retrospective study enrolled 14 consecutive patients diagnosed with ethambutol induced optic neuropathy among cases of pulmonary and extra pulmonary tuberculosis treated with Antitubercular therapy with ethambutol from 1st April 2022 to 30th March 2024 presenting to the ophthalmology department at B. P. Koirala Lions Centre for Ophthalmic Studies, a tertiary eye centre in Nepal. There were 3 cases excluded after alternative diagnosis, 1 of linezolid induced optic neuropathy, 1 case of tuberculous optic neuropathy and 1 with optochaismatic arachnoiditis. Ethical approval was obtained from the Institutional Review Committee (IRC) of Institute of Medicine(IOM), Tribhuvan Universtity.

The patients taking antitubercular treatment for tuberculosis having ocular symptoms were referred to the ophthalmology department. Ethambutol induced optic neuropathy was diagnosed by a neuro-ophthalmologist when a patient developed bilateral painless subacute visual loss (reduced visual acuity, abnormal color vision and/or visual field defect) only after the start and while on ethambutol therapy and any other possible cause of visual dysfunction (glaucoma, retinal diseases or other causes of optic neuropathy) was ruled out. Patients with CNS TB, vision loss due to other neurological causes, Tuberculous optic neuropathy/ optochiamatic arachnoiditis, intraocular tuberculosis and patients under linezolid were excluded in this study. In cases where there was suspicion for other causes of optic neuropathy, alternative diagnosis was ruled out by Brain neuroimaging and appropriate blood investigations.

For any case of ethambutol induced optic neuropathy, ethambutol was stopped immediately and the patient was sent to the treating physician regarding the need to start second line treatment and the patient was started on supplements with multivitamins B group with copper and zinc.

Demographic profile (age, gender, ethnicity), ethambutol dosage and duration, type of TB, duration of symptoms, body weight and any other systemic diseases and its treatment were recorded in the pre-designed proforma. Best corrected visual acuity (BCVA) was recorded using a Snellen chart. Anterior and posterior segment examination was done by slit lamp biomicroscope with a 90 D lens. Color vision and contrast sensitivity were assessed on Farnsworth D-15 chart and Pelli Robson contrast sensitivity Chart respectively. Reports of retinal nerve fiber layer (RNFL) thickness and ganglion cell layer thickness (GCC) were obtained from Optovue optical coherence tomography machine, Goldman visual field (GVF) and visual evoked potential (VEP) were recorded if these were available for the patient.

Statistical Analysis

Collected data was checked, reviewed, and organized for completeness and accuracy. The data was entered in the Statistical Package for Social Science (SPSS) version 26 for analysis. The age and gender distribution of the study sample was tested by descriptive statistics data analysis. One-sample t-test and independent sample t-test were used for comparison of mean. A p-value less than 0.05 was considered statically significant.

## RESULTS

A total of 28 eyes of 14 patients who developed EON were studied, where 64% (n-9) were males whereas females were 36% (n-5). Their mean age was 50.64± 15.8 years (range 25-78 years). Majority of the patients, 50% (n-7) were aged 51 to 60 years. The mean dose of ethambutol among patients developing EON was 18.27 ± 2.29 mg/kg (minimum dose of 16.6mg/kg and maximum of 21.15 mg/kg). There was bilateral involvement in all patients. The toxicity occurred after a mean duration of 7.25± 3.45 months (minimum 4 months, maximum 18 months).Majority of patients (50%) were diagnosed with bone tuberculosis (n-7 patients), dissemated tuberculosis in 21%, pulmonary tuberculosis and pott's spine in 14%(n-2) followed by tuberculous pericarditis and genito urinary tuberculosis in 7% (n-1) respectively as show in table I.

Seventy-five percent cases (n-21 eyes) had visual acuity less than 20/120, of which 50% (n-14) has best corrected visual acuity worse than 20/200. Colour vision and contrast sensitivity could be assessed in subjects with visual acuity better than 20/200, that is 14 eyes (n-7 patients). On fundus examination, optic disc revealed temporal pallor in 57% (n-16 eyes), pale disc in 7% (n-2 eyes), hyperemic disc in 7% (n-2 eyes) and normal disc in 29% (n-8 eyes).

Variable pattern of color vision deficit was noted with tritan color vision defect in four eyes, nonspecific defect was seen in six

eyes and color vision within normal limit in four eyes. The mean contrast sensitivity in the group was 1.50±0.32 log units which is significantly reduced compared to the normal range. Similarly, visual field report was available for only eight eyes, where six eyes had cecocentral scotoma and two eyes had enlarged blind spot on kinetic perimetry.

**Table 1:** Demographics and clinical profile of Ethambutol induced optic neuropathy patients.

| Characteristics | Frequency |
|---|---|
| Age | Mean: 50.64± 15.8 years (range 25 to 78 years) |
| Gender (male/female) | 9 (64.3%) male/ 5 (35.7%) female |
| Ethambutol dose | Mean: 18.27 ± 2.29 mg/kg |
| Ethambutol Duration | Mean: 7.25± 3.45 months |
| Visual Acuity (n-28 eyes)<br>a. 20/60<br>b. 20/80<br>c. 20/120<br>d. ≤ 20/200 | <br>5 (17.86%)<br>2 (7.14%)<br>7 (25%)<br>14 (50%) |
| Type of Tuberculosis (n-14 patients)<br>a. Bone Tuberculous<br>b. Dissemated Tuberculosis<br>c. Pulmonary Tuberculosis(retreatment)<br>d. Tuberculous Pericarditis<br>e. Genito Urinary Tuberculosis | <br>7 (50.0%)<br>3 (21.4%)<br>2 (14.3%)<br>1 (7.15%)<br>1 (7.15%) |
| Color Vision (n-14 eyes)<br>a. Normal<br>b. Tritan<br>c. Non-specific | <br>4<br>4<br>6 |
| Contrast Sensitivity (n-14 eyes) | Mean: 1.50±0.32 log units |
| Visual Field (n-8 eyes)<br>a. cecocentral scotoma<br>b. enlarged blind spot | <br>6<br>2 |
| Disc (n-28 eyes)<br>a. Normal<br>b. Temporal Pallor<br>c. Pale disc<br>d. Hyperemia | <br>8 (28.57%)<br>16 (57.15%)<br>2 (7.14%)<br>2 (7.14%) |

The mean average RNFL thickness in the right eye was 100.75 ± 16.27 µm and 98.25±14.81 µm in the left eye, which is within normal range of thickness. Similarly, the mean average GCC was 82.00±13.00 µm and 86.87±12.17 µm in the right and left eye respectively, which significantly thinner than normal thickness. The details of RNFL and GCC thickness have been shown in table II. Delayed mean P 100 latency was seen for both high and low frequencies and decrease in amplitude was noted in both high and low frequencies was noted in Visual Evoked Responses as shown in table III.

**Table 2:** Retinal nerve fibre layer (RNFL) and Ganglion cell layer (GCC) thickness of right and left eyes

| Retinal parameters | Right Eye (µm) | Left Eye (µm) |
|---|---|---|
| Average RNFL thickness | 100.75±16.27 | 98.25±14.81 |
| Superior RNFL thickness | 102.37±16.19 | 100.62±13.65 |
| Inferior RNFL thickness | 99.00±17.3 | 95.87±16.72 |
| Average GCC thickness | 82.00±13.00 | 86.87±12.17 |
| Superior GCC thickness | 82.12±13.15 | 87.00±13.54 |
| Inferior GCC thickness | 82.12±13.62 | 86.50±12.27 |

**Table 3:** Visual evoked potential parameters

| VEP parameters | Right Eye | Left Eye |
|---|---|---|
| P 100 latency, High frequency (ms) | 142.03±11.81 | 144.11±9.77 |
| P 100 latency, Low frequency (ms) | 137.93±15.80 | 139.59±9.49 |
| N75-P100 Amplitude, High Frequency (µV) | 4.17±2.35 | 4.37±2.15 |
| N75-P100 Amplitude, Low frequency (µV) | 3.86±1.58 | 3.83±2.64 |

RNFL was compared with presenting visual acuity and it was found that there was a statistically significant difference in Average RNFL (OD) and Superior RNFL (OD) between cases presenting with Visual Acuity of >20/200 and less than 20/200. Similarly there was also a statistically significant difference between Average GCC (OS) and Superior GCC (OD and OS) between cases presenting with Visual Acuity of >20/200 and less than 20/200. All cases with visual acuity less than 20/200 had thinner RNFL and GCC even though it was not statistically significant.

**Table 4:** Comparison of Retinal Nerve Fibre Layer thickness in patients with Visual Acuity(VA) ≥ 20/200 and 20/200

| RNFL parameters (µm) | VA ≥ 20/200 | VA < 20/200 | t | P |
|---|---|---|---|---|
| Avg RNFL (OD) | 112.0±13.11 | 89.50±10.40 | 2.68 | 0.036* |
| Avg RNFL (OS) | 107.50±14.79 | 89.00±8.04 | 2.19 | 0.07 |
| Sup RNFL (OD) | 114.25±11.44 | 90.50±10.24 | 3.09 | 0.021* |
| Sup RNFL (OS) | 108.7±14.40 | 92.5±7.18 | 2.01 | 0.09 |
| Inf RNFL (OD) | 110.00±15.85 | 88.00±11.16 | 2.26 | 0.064 |
| Inf RNFL (OS) | 106.25±16.07 | 85.5±10.37 | 2.16 | 0.06 |

| | | | | |
|---|---|---|---|---|
| Avg GCC (OD) | 89.50±12.87 | 74.5±8.88 | 1.91 | 0.104 |
| Avg GCC (OS) | 95.75±6.65 | 78.00±9.55 | 3.04 | 0.023* |
| Sup GCC (OD) | 91.25±9.97 | 73.00±9.05 | 2.70 | 0.008* |
| Sup GCC (OS) | 97.75±4.50 | 76.25±9.97 | 3.92 | 0.008* |
| Inf GCC (OD) | 88.50±16.11 | 75.75±8.05 | 1.41 | 0.207 |
| Inf GCC (OS) | 93.50±10.66 | 79.50±10.34 | 1.88 | 0.108 |

**Table 5:** Comparison of Visual Evoked Potential(VEP) parameters in patients with Visual Acuity(VA) ≥ 20/200 and < 20/200

| VEP parameters | VA ≥ 20/200 | VA ≤ 20/200 | t | P value |
|---|---|---|---|---|
| P 100 latency, High frequency (RE) | 136.26±12.97ms | 147.80±7.90 | -1.69 | 0.128 |
| P 100 latency, High frequency (LE) | 139.74±11.34ms | 148.48±6.21 | -1.51 | 0.169 |
| P 100 latency, Low frequency (RE) | 108.7±14.40ms | 92.5±7.18 | -0.88 | 0.40 |
| P 100 latency, Low frequency (LE) | 133.44±17.68ms | 142.42±14.09 | -2.34 | 0.047* |
| N75-P100 Amplitude, High Frequency (RE) | 3.52±2.47µV | 4.83±2.28 µV | -0.86 | 0.411 |
| N75-P100 Amplitude, High Frequency (LE) | 4.43±2.30 µV | 4.31±2.26 µV | 0.086 | 0.934 |
| N75-P100 Amplitude, Low frequency (RE) | 3.26±1.69 µV | 4.47±1.36 µV | -0.124 | 0.24 |
| N75-P100 Amplitude, Low frequency (LE) | 2.62±2.49 µV | 5.03±2.42 µV | -0.154 | 0.16 |

VEP parameters was compared with presenting visual acuity and it was found that there was a statistically significant difference in P 100 latency, Low frequency (LE) between cases presenting with Visual Acuity of > 20/200 and less than 20/200.

No statistically significant correlation was found between duration of loss of vision noted by patients(chronicity) and duration of intake of ethambutol with OCT and visual evoked potential parameters.

50% patients followed up at 6 months. Patients with visual acuity >20/200 (n-4) showed an improvement of 2 or more lines but patient with <20/200 (n- 2) had only one line improvement in visual acuity and 1 patient with VA of CFCF had no improvement in visual acuity.

## DISCUSSION

Ethambutol induced optic neuropathy manifesting as partially reversible optic neuropathy with variable loss of visual functions may lead to potentially permanent vision loss. Currently, there is no effective treatment for ethambutol-induced toxic optic neuropathy. Ocular toxicity is related to dose and duration of treatment with the incidence being as high as 18% in patients receiving >35 mg/kg/day, 5-6% with 25 mg/kg/day, 3% with 20 mg/kg per day and <1% with 15 mg/kg/day of EMB, when receiving for more than two months.10 Even though a dose of 15-20 mg/kg per day is deemed safe and effective, in our study patients taking ethambutol at a mean dose of 18.27 ± 2.29 mg/kg/day for a mean duration of 7.25± 3.45 months developed optic neuropathy. This effect is generally reversible after drug discontinuation promptly but few patients develop permanent irreversible vision loss and ocular changes despite drug cessation.[11]

Current national guidelines have acknowledged that ethambutol may lead to difficulty with vision as a major side effects and recommended that prolonged usage of ethambutol(more than 2 months) be used only for complicated/severe extra pulmonary diseease(CNS TB, Musculoskeletal TB, TB pericarditis, Miliary TB etc) and retreatment cases.[12] The treatment of drug resistant TB(DR TB) is more challenging where Ethambutol maybe required for a prolonged duration. Another drug used for DR TB, Linezolid is known to cause peripheral neuropathy and also has been known to cause optic neuropathy.[13] So in patients receiving both the drugs, ethambutol and linezolid it might be wise to stop both the drugs if patients develop blurring of vision. In this study we excluded patients taking linezolid. Fifty percent of the cases of EON in our study were treated for bone TB which is a common form of severe extra pulmonary TB(EPTB) requiring prolonged ethambutol usage. The patients with bone TB and other forms of serious diseases often maybe limited in independent mobility leading to delayed diagnosis and worse visual function at presentation. Awareness about EON and early detection and stopping of ethambutol may help in preventing further deterioration of visual functions.

The mean age of patients with EON in our study was 50.64± 15.8 years (range 25-78 years). Previous studies like Chen et al. have reported that older aged people (65.4±15.9 years in their study), were at higher risk factor for the occurrence of EON.[14] Moreover, excessive smoking and particularly presence of renal diseases play an important role for occurrence of EON, as approximately 70% of each ethambutol dose is excreted by the kidneys. In instances of renal insufficiency, serum levels of ethambutol may

increase, leading to an increased risk of toxicity.[15-17] However none of the cases in our study had impaired renal function.

In our study, 75% of cases(n-21 eyes) had vision impairment less than 20/120, of which 50% (n-14 eyes) had vision less than 20/200 in Snellen's acuity chart. Ethambutol results in bilateral progressive painless loss of vision and commonly central or cecocentral scotoma due to papillomacular dysfunction, however peripheral visual field defect, altitudinal field defects, and bilateral temporal field defects occasionally reported, but sometimes may also have normal visual fields.[15-18] In our study visual fields could be done in only 8 eyes, and in the rest of the eyes visual fields could not be performed due to poor vision. The most common visual field defect was cecocentral scotoma (n-6) followed by enlarged blind spot(n-2).

Ethambutol causes visual dysfunction which can range from reduced visual acuity, color vision, reduced contrast sensitivity, defects in visual field and changes in VEP parameters.[8,19] Dyschromatopsia has been known to be an early sign of toxicity, and blue-yellow(tritan) color changes were reported to be common in one study.[11] However, in our study nonspecific color vision defect was seen in 6 cases followed by tritan anomaly(n-4). Mean contrast sensitivity was decreased (1.50±0.32 log units) in our study. Some studies indicate that loss of color vision and contrast sensitivity may not be an early marker of EON.[20-22]

The optic disc looks normal in the early stages of ethambutol-induced optic neuropathy and observation of pallor of the optic nerve indicates chronicity of the toxicity and has been thought to be a poor prognostic indicator.[2] In our study, we observed pallor in 64% (n-18 eyes) which correlated to the <20/200 presenting visual acuity(VA) in 50% of the patients indicating chronic damage of the optic nerves. Only 50% patients followed up at 6 months after stopping ethambutol and patients with presenting VA >20/200 showed more likelihood of improvement of final VA which was consistent with previous studies.[23,24]

In the recent times, OCT and Electrophysiological tests like VEP and ERG have been found to be more sensitive for detection of early or even subclinical toxicity due to ethambutol.[18,21,22,25] We noted mean average RNFL thickness to be 100.75±16.27 µm and 98.25±14.81 µm, which is within the normal range, but Ganglion cell complex (GCC) thinning was seen. Some other studies have also reported normal or even slightly increased RNFL thickness, with thinning of the GCC in the early stages.[21,26-28] However some studies have shown thinning of the RNFL, more pronounced in the temporal quadrant.[29] When RNFL was compared among cases with presenting visual acuity >20/200 and less than 20/200, it was found that there was a statistically significant thinning of Average RNFL (OD) and Superior RNFL (OD) between cases presenting with Visual Acuity. Similarly, the thinning of the GCC was more marked in patients with presenting VA <20/200.

Visual evoked potential (VEP) is an objective test to detect abnormalities from photoreceptors to the cortex of the occipital lobe. EON has been shown to cause a delay in axoplasmic transport because of axonal swelling or myelin thinning VEP is helpful for detecting toxic optic neuropathy. We observed significantly increased latency in P100 wave and decreased amplitude in the patients with optic neuropathy which was similar to previous studies[22,28] where it was reported that the delay in P100 latency was observed even in asymptomatic patients after taking ethambutol. In our study, we also found that the delay in P 100 latency and decrease in amplitudes was more marked in cases presenting with Visual Acuity of > 20/200.

The exact pathophysiological mechanism underlying EON is still unclear. Ethambutol causes disrupted oxidative phosphorylation secondary to decreased available copper in the human mitochondria, or from inhibited lysosomal activation due to zinc chelation causing impairment of axonal transport in the optic nerve and thus lead to optic neuropathy.[25,30,31] There is no known effective treatment for EON, apart from stopping EMB immediately in all cases. The vision may gradually recover in some cases, but the damage can also be irreversible. Therefore, a high index of suspicion of EON is required to timely diagnose ocular toxicity in all patients taking ethambutol.

## CONCLUSION

Ethambutol can cause severe visual impairment, which may be either reversible or irreversible. In our study patients taking ethambutol at a mean dose of 18.27 ± 2.29 mg/kg/day for a mean duration of 7.25± 3.45 months developed EON. Fifty percent patients had a presenting visual acuity of <20/200. Patients with presenting visual acuity <20/200 also had thinner RNFL and GCC in OCT analysis and more marked increased in P100 latencies and decrease in amplitudes compared to patients with presenting VA >20/200. Regular examinations and monitoring of visual function and cessation of drug at the earliest evidence of EON may reduce the chances of irreversible damage.

**LIMITATIONS OF THE STUDY:** Our small sample size and retrospective design limit generalizability of the findings. Future prospective studies with larger cohorts and multicenter collaboration are needed.

**FINANCIAL DISCLOSURE:** None

**CONFLICT OF INTEREST:** None

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