Purpose: Ethambutol (EMB) is one of the first-line drugs used for treating tuberculosis. Vision loss due to optic nerve toxicity is a well-known potential side effect of the drug. Our aim was to evaluate the clinical features and visual outcomes of patients with EMB optic neuropathy (EON). Methods: A retrospective, observational, single-center study of all patients who were diagnosed to have EON during January 2017–December 2019 was done. All these patients were screened in the Department of Neuro-ophthalmology at a referral tertiary eye care institution in India. Clinical features, visual outcomes, and neuroimaging findings of these patients were analyzed. Results: Two hundred and fifty-six eyes of 128 patients were included. Of these, 73 were male and 55 were female. Mean age was 50.55 ± 15 years. Mean visual acuity at presentation was 1.12 ± 0.45 logarithm of the minimum angle of resolution (logMAR). One hundred and forty three eyes had normal optic disk on presentation, 111 had disk pallor, and two eyes had disk edema. The most common field defect was central/paracentral scotoma (26.2%) followed by temporal defects (24.6%). Magnetic resonance imaging (MRI) brain and orbit showed optic nerve signals in 19.6% and chiasmal signals in 5.2%. At the final follow-up, a ≥2-line vision improvement was noted in 161 eyes (62.9%), which was statistically significant. Conclusion: Multiple prognostic factors were analyzed to predict the visual recovery of EON. We observed that patients presenting with visual acuity worse than 6/60 had poor visual outcome and long duration of follow-up showed better visual recovery, proving the possibility of a gradual recovery pattern of EON. Interestingly, we found in our study that the chances of favorable visual outcome were directly proportionate to early diagnosis and cessation of EMB.

Key words: Bitemporal defects, chiasm, ethambutol (EMB), ethambutol optic neuropathy (EON), MRI, pallor, tuberculosis

Ethambutol (EMB) is a bacteriostatic antibiotic that is used, in combination, in the treatment of infections caused by the Mycobacterium group of organisms, most commonly tuberculosis (TB). It has been used widely in anti-tubercular treatment since 1960, and its ability to cause visual disturbances has been documented since then.[1] According to recent literature, the worldwide prevalence of EMB optic neuropathy (EON) is 1%–2% per year,[2] and it affects approximately 100,000 people worldwide each year.[3] According to the World Health Organization’s (WHO) Global TB report of 2019, India accounted for more than a quarter of the new TB cases in the world. Apart from cessation of the drug, there is currently no effective treatment for EON. However, early recognition and discontinuation of the drug may prevent further deterioration of visual function.[4] The purpose of this study is to evaluate the clinical features and visual outcomes of patients with EON.

Methods

A retrospective chart review and analysis of all patients diagnosed to have EON from January 2017 to December 2019 at a tertiary eye care institution in South India and who fulfilled the inclusion criteria was done.

Inclusion criteria

1. Patients diagnosed clinically to have EON by a neuro-ophthalmologist
2. History of anti-TB treatment with EMB hydrochloride within 1 year of onset of visual symptoms
3. No other associated ocular cause for the visual loss
4. At least one follow-up after the initial presentation and stopping the EMB treatment.

Exclusion criteria

1. History of stopping EMB more than 1 year before presentation
2. Patients with other ophthalmic manifestations of TB or central nervous system (CNS) TB.

All patients’ demographic profiles, dose and duration of EMB, clinical features, and visual responses with and without...
EMB were noted. The vision was recorded using a Snellen chart, and the logarithm of the minimum angle of resolution (logMAR) equivalent was calculated. Color vision was tested using Ishihara plates. Optic disk appearance was noted by slit-lamp biomicroscopy as well as indirect ophthalmoscopy with a 20 D lens. Humphrey’s visual field (HVF) test was noted if it was done for the patient. Magnetic resonance imaging (MRI) of brain and orbit, visual evoked potential (VEP), serum zinc levels if done, and treatment offered on presentation were recorded. Patients who were on EMB were advised to discontinue the medication and switch to alternate TB treatment regimens, under the guidance of a referral infectious disease consultant, and were started on zinc tablets and neuro vitamins (B complex vitamin supplements) for a period of 6–9 months. Zinc tablets containing 10 mg zinc and neuro vitamins (vitamin B complex containing thiamine mononitrate 10 mg, riboflavin 10 mg, pyridoxine hydrochloride 3 mg, cyanocobalamine 15 mcg, nicotinamide 45 mg, calcium pantothenate 50 mg) were used. Favorable visual outcome was defined as 22-line improvement on the Snellen chart at the final follow-up. Institutional review board and ethics committee clearance were obtained, and the study met the tenets of Declaration of Helsinki.

Statistical analysis
Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) version 23 was used for statistical analysis. The logarithm of reciprocal decimal visual acuity (VA) was used to approximate logMAR. Logistic regression analysis was used to evaluate the association between visual outcome in various subgroups, such as age, gender, comorbid conditions, onset of vision problem, duration of EMB discontinued, presenting VA, initial disk findings, visual evoked response (VER), visual outcome with zinc and neuro vitamin supplements, and duration of follow-up. The outcome variable was an improvement in the final VA of ≥2 Snellen’s lines, and a P value of <0.05 was considered statistically significant.

Results
A total of 256 eyes of 128 patients who fulfilled the inclusion criteria were studied. Of 128 patients, 73 (57.03%) were male and 55 were female (42.96%). The mean age on presentation was 50.55 ± 15 years, with the oldest patient being 81 years and the youngest being 15 years. Also, 107 patients (83.59%) were less than 65 years of age. The mean duration of vision loss on presentation was 65.42 ± 59.7 days. All our patients diagnosed with TB received EMB as a fixed-dose combination. Indian literature quotes 275 mg/day, but the total number of tablets varies with weight. Most of our patients received 800 mg/day. The mean duration of EMB intake before the onset of symptoms was 7.5 ± 3.88 months (range, 2–36 months). All patients had bilateral involvement. Acute onset was defined as visual deficit ≤6 weeks and chronic onset as visual deficit >6 weeks. Fifty-nine patients had acute onset of symptoms, while 69 patients had a chronic presentation. The mean duration of follow-up was 7.8 ± 9.1 months (range, 1–57 months).

The mean vision on presentation was 1.12 ± 0.45 logMAR. Also, 66.4% (n = 85, 170 eyes) of patients had vision of less than 6/60. Color vision was recorded in 219 eyes (114 patients). Color vision was defective in 184 eyes (71.8%) and the remaining (35 eyes) had normal color vision. The mean initial VA for 35 eyes with normal color vision was 0.73 ± 0.42. Of 256 eyes, 143 eyes had normal optic disks on presentation, 111 eyes had disk pallor, and two eyes had disk edema. Visual fields were done in 225 eyes (114 patients). The remaining patients were unable to perform visual fields in view of poor VA. Patients with VA <6/60, who were unable to perform visual fields with size III stimulus were given a larger target size (stimulus V) to perform the visual field. The most common field defect was paracentral and central scotoma (67 eyes, 26.2%), followed by temporal field defects; 63 eyes (24.6%) had bitemporal field defects. VEP at the time of presentation was done in only 60 patients (80 eyes). Thirty-four eyes (42.5%) had reduced amplitude, while 23 eyes (28.7%) had delayed P1 latency and four eyes (5%) had both reduced amplitude and delayed latency. Extinguished VEP response was noted in two eyes (2.5%). Optical coherence tomography (OCT) data of retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness at presentation was available only for four patients. Since this is a retrospective study, not many patients underwent OCT. All four had normal RNFL thickness, while GCC thinning was noted in two patients and the remaining two had normal GCC thickness. MRI brain and orbit was done in 96 patients of whom 54 patients had normal imaging. In 34 patients, T2-hyperintense signals were noted in optic nerves, chiasm, and optic tracts. Eight patients had thinned out optic nerves. The MRI findings are described in Table 1.

### Table 1: Demographics and clinical profile of our study cohort

| Characteristics                        | No. (%)       |
|----------------------------------------|---------------|
| Age (years)                            | 50.55±15 (range: 15-81) |
| Gender (male/female)                   | 73 (57.03%)/55 (42.96%) |
| Follow-up duration (months)            | 7.8±9.1 months (range: 1-57 months) |
| Mean duration of intake of medication  | 7.5±3.88 months (range: 2-36 months) |
| Bilateral involvement                  | 128 patients (100%) |
| Onset of vision loss                   |               |
| Acute                                  | 59 (46.09%)  |
| Chronic                                | 69 (53.9%)   |
| Mean vision on presentation (logMAR)   | 1.12±0.45     |
| Optic disk appearance (eyes)           |               |
| Normal                                 | 143 (55.8%)  |
| Pallor                                 | 111 (43.3%)  |
| Edema                                  | 2 (0.78%)    |
| Visual field defects (eyes)            |               |
| Central/paracentral                    | 67 (26.2%)   |
| Bitemporal                             | 63 (24.6%)   |
| Underlying systemic disease (patients) |               |
| Diabetes mellitus                      | 48 (37.5%)   |
| Hypertension                           | 33 (25.8%)   |
| MRI findings (n=96 patients)           |               |
| Normal                                 | 54 (55.7%)   |
| Optic nerve signals                    | 19 (19.6%)   |
| Chiasmal signals                       | 5 (5.2%)     |
| Thinned out optic nerves               | 8 (8.2%)     |
| Optic nerve signals + chiasmal signals | 6 (6.2%)     |
| Chiasmal signals + optic tract signals | 4 (4.1%)     |

logMAR=logarithm of the minimum angle of resolution, MRI=magnetic resonance imaging.
All patients had received zinc supplements (n = 121), except seven patients who were treated only with neuro vitamins (n = 7). Of 121 patients, 47 patients were treated with a combination of zinc supplements and neuro vitamins. The mean vision on the final follow-up was 0.65 ± 0.56 logMAR. Also, 161 eyes of 81 patients (62.9%) showed two or more lines improvement on the Snellen chart. The color vision improved to normal in 69 eyes (43.4%). Visual fields improved in 96 eyes (55.5%) and were stable in 68 eyes (39.3%).

Multiple prognostic factors were analyzed in our cohort to predict visual recovery after discontinuation of EMB [Table 2]. Risk factors for poor recovery included older age, hypertension, diabetes mellitus, and disk pallor on presentation, though they were not statistically significant. Initial VA worse than 6/60 showed a poor visual outcome, but it was also statistically insignificant. Patients who presented with acute onset of symptoms, female gender, and those having a longer duration of follow-up had a better outcome. It was found that when the duration of EMB stopped was within 2 weeks, there was a significant improvement in the final visual outcome.

Discussion

WHO-recommended daily dosage of EMB for TB is 15–20 mg/kg/day, and at the current dose, the incidence of EON is 1%–3%. All our patients were on a dosage of between 15 and 25 mg/kg/day. Chen et al. found that age above 65 years was a risk factor for the occurrence of EON. In another meta-analysis of 70 patients with EON, 40% of the patients were over 65 years; however, in our study, only 21 patients (26.9%) were above 65 years.

EON is described in patients on EMB therapy for at least 6–7 months and is very rare before 2 months of medication. In our study, five patients developed symptoms within 2 months of EMB treatment. None of them had any risk factors that could explain the early onset of EON. The average onset of EON in our study was 7.5 ± 3.88 months (range, 2–36 months) after initiation of EMB treatment. Literature reports show optic nerve toxicity can occur as early as 1.5 months and as late as 12 months after the onset.[8,9] Lee et al. also reported a similar range of development of visual symptoms from 1 to 36 months.

In our study, 161 of 256 eyes (62.9%) showed two or more improvement on the Snellen chart at the final follow-up. Sivakumar et al. reported that three of four patients with EON improved after cessation of EMB and one had permanent loss of VA at 1-year follow-up. The recovery rate was 50% in a study done by Chen et al. Kumar et al. showed 42.2% had a visual recovery better than 20/200. Thus, visual recovery in our study was comparable to previous reports in the literature. Woung et al. reported visual recovery of EON within 3–4 months of stopping the drug. In our cohort, we compared the visual recovery in patients with less than 1 year of follow-up and more than 1-year follow-up. The mean final VA of patients with less than 1-year follow-up was 0.68 ± 0.56 and with more than 1-year follow-up was 0.51 ± 0.59 (P = 0.016). We observed a significant difference in the final VA between patients with less than and more than 12 months of follow-up, proving the possibility of a gradual recovery pattern.

Visual field defect in EON is usually a central or cecocentral scotoma due to papillomacular dysfunction. Similar to previous studies, the most common visual field defect was central/paracentral scotomas (67 eyes). However, bitemporal defects have been described due to selective damage to the nasal crossing fibers in the optic chiasm, and in our study, bitemporal defects were seen in 63 eyes. Among patients who underwent VEP in our study, 42.5% had reduced amplitude and delayed latency was seen in 28.7%. Yiannikas and Srivastava et al. showed both delayed latency and amplitude changes. However, in the study by Menon et al. and Kim et al., latency was affected more compared to amplitude, as they described subclinical toxicity even before the loss of VA. On MRI brain and orbit, chiasmal, optic nerve, and optic tract T2-hyperintense signals were noted. However, few patients had normal MRI [Table 1]. MRI was advised for all patients, particularly when there were dense cecocentral and temporal defects, to rule out inflammatory optic neuropathies, chiasmal arachnoiditis, and other possible causes of optic neuropathies before confirming the diagnosis of EON. MRI brain was done to exclude CNS involvement like basal arachnoiditis and TB meningitis. In this EON cohort, we observed isolated chiasmal signals without thickening of the chiasm, which has also been reported earlier. Very few studies have described optic chiasmal involvement on MRI in patients with EMB-induced toxic optic neuropathy. Osaguna et al. have reported a case with hyperintense signal in the optic chiasm on MRI brain. Geyer et al. also have documented a case with hyperintense signal in chiasm and proximal optic tracts due to EMB toxicity.

We studied the risk factors for EON and its effect on visual outcome. Tsai et al. had reported that visual recovery was poor in patients above 60 years of age, similar to our study, as patients ≥65 years showed poor visual outcome, though not statistically significant. Age as a risk factor was evaluated by Chen et al. which concluded that elderly patients had poor visual recovery from EMB toxicity. Therefore, elderly patients on EMB treatment needs close monitoring of vision. Chen

### Table 2: Analysis of risk factors for visual outcome

| Variables                        | Odds ratio | 95% Confidence interval | P       |
|----------------------------------|------------|-------------------------|---------|
| Follow-up: 6 months-1 year       | 1.714      | 0.891–3.296             | 0.106   |
| Follow-up: >1 year               | 2.011      | 1.086–4.104             | 0.05    |
| Age ≥65 years                    | 0.843      | 0.429–1.658             | 0.622   |
| Female                           | 1.213      | 0.725–2.03             | 0.461   |
| Diabetes mellitus                | 0.954      | 0.457–1.643             | 0.92    |
| Hypertension                     | 0.902      | 0.403–2.016             | 0.801   |
| Initial VA worse than 6/60       | 0.585      | 0.336–1.022             | 0.059   |
| Disk pallor                      | 0.734      | 0.44–1.225              | 0.237   |
| Acute onset                      | 1.383      | 0.829–2.309             | 0.215   |
| Duration of EMB discontinued within 2 weeks | 2.29 | 1.071–5.405 | 0.047 |
| VER: reduced amplitude           | 10.8       | 9.13–12.7              | 0.059   |
| VER: latency delay               | 6.27       | 5.08–14.4              | 0.130   |
| Patients who received drug combination (zinc tablets with neuro vitamins) | 1.25 | 0.728–2.141 | 0.419 |

EMB = ethambutol, VA = visual acuity, VER = visual evoked response
et al.,[11] in their study, did not find a statistically significant difference based on initial VA between patients with and without vision improvement. However, in our study, we noted patients with initial VA worse than 6/60 showing poor visual outcome, though statistically insignificant. Underlying systemic diseases like hypertension and diabetes mellitus showed an odds ratio near 1, indicating that these factors were not strongly associated with a favorable prognosis, consistent with previous studies,[6,11] but it was not statistically significant. EMB toxicity is known to be associated with renal disorders. Being a retrospective study in nature, all our patients had a recorded history of systemic illnesses in the electronic medical records, of which only one patient was documented to have renal disorder (nephrotic syndrome). Hence, analyzing the correlation between renal disorder and risk of EMB toxic optic neuropathy with one sample was not possible. Optic atrophy on presentation proved to be a poor prognostic indicator.[5] In our study, 43.3% had disk pallor on presentation. Patients with disk pallor had poor recovery, but it was not statistically significant. Lee et al.[10] also showed that none of the patients (n = 6) with disk pallor on presentation had visual improvement, indicating poor prognosis. We analyzed the effect of VER on the visual outcome. The odds ratio for a favorable visual outcome was 10.8-fold for those with reduced amplitude, while it was 6.27 with delayed latency. Compared to eyes with both amplitude reduction and delayed latency, better recovery was seen in those with amplitude reduction > latency delay. However, this analysis was not statistically significant. Early discontinuation of EMB showed a favorable visual outcome, which was statistically significant. Several studies[10,19,22] have reported visual improvement over a course of time when EON was detected early and the drug discontinued. Tsai et al.[22] reported 50% visual recovery after 1–3 years of follow-up. The recovery time after discontinuation of EMB ranged from 1 to 12 months in the study by Woung et al.,[13] with a maximum follow-up of up to 44 months. Our study showed that the odds ratio for visual recovery was 2.011-fold for those with a longer duration of follow-up. However, further longitudinal analysis of the same cohort is required to assess the relevance of visual recovery with long-term follow-up. We assessed the outcome of patients who received zinc supplements and those who were treated with a combination of zinc and neuro vitamins. We noted 22-line improvement in 60.8% of the eyes treated with zinc supplements and 66% of the eyes treated with zinc and neuro vitamins combination, indicating that the drug combination had a better outcome, but it was statistically insignificant.

Apart from stopping the drug, there is no known effective treatment for EON. It has been hypothesized that EON results from inhibited lysosomal activation due to the chelation of zinc[23] or disrupted oxidative phosphorylation secondary to decreased available copper in human mitochondria,[40] and patients with low plasma zinc levels have been found to have a higher likelihood of developing EON.[23] Apart from seven patients, all our patients received zinc supplements for 3 months or more. Serum zinc levels were available for 10 of our patients, out of which four had reduced amounts. Further prospective research is required to analyze the correlation between serum zinc levels and the tendency to develop EON.

**Limitations**

Being retrospective in nature, the study has its own limitations. Electrophysiological tests were not performed in all patients, and none had contrast sensitivity assessment. There was variability in the duration of follow-up for different patients. Though the sample size was large, it is a single-center study analyzing the data of patients belonging to same ethnicity, and hence, the results may introduce bias. Concurrent toxicity with isoniazid could not be ruled out, and lack of randomization was another limiting factor.

**Conclusion**

Optic neuropathy is not uncommon following antitubercular therapy with EMB. India being an endemic country for TB, significant use of this drug is not surprising.

In our study, the visual outcome was favorable in 62.9% (161 eyes) during the final follow-up, and the most common field defect was central/paracentral scotoma followed by bitemporal defects. Visual recovery in our cohort showed a slow recovery pattern, as patients with a longer duration of follow-up had better outcome. EMB optic neuropathy is a major concern in antitubercular therapy, as it can cause significant visual impairment and can also be irreversible in few instances. Early detection and discontinuation of the drug can prevent devastating vision loss.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Carr RE, Henkind P. Ocular manifestations of ethambutol, toxic amblyopia after administration of an experimental antituberculous drug. Arch Ophthalmol 1962;67:566-71.
2. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol optic neuritis. Curr Opin Ophthalmol 2017;28:545-51.
3. Sadun AA, Wang MY. Ethambutol optic neuropathy: How we can prevent 100,000 new cases of blindness each year. J Neuroophthalmol 2008;28:265-8.
4. Saxena R, Phuljhele S, Prakash A, Lodha R, Singh D, Karma S, et al. The Inosrg. ethambutol optic neuropathy: Vigilance and screening, the keys to prevent blindness with the revised anti-tuberculosis therapy regimen. J Assoc Physicians India 2021;69:54-7.
5. Chen HY, Lai SW, Muo CH, Chen PC, Wang II. Ethambutol-induced optic neuropathy: A nationwide population-based study from Taiwan. Br J Ophthalmol 2012;96:1368-71.
6. Talbert Estlin KA, Sadun AA. Risk factors for ethambutol optic toxicity. Int Ophthalmol 2010;30:63-72.
7. Phillips PH. Toxic and deficiency optic neuropathies. In: Miller NR, Newman NJ, editors. Bioulse V, Kerrison JB, associate editors. Walsh and Hoyt’s Clinical Neuro-ophthalmology. 6th ed. Baltimore, Maryland: Lippincott Williams and Wilkins; 2005. p. 4556e.
8. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. Mayo Clin Proc 2003;78:1409-11.
9. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from ethambutol: A review of 4 cases and recommended precautions. NZ Med J 1998;111:428-30.
10. Lee EJ, Kim SJ, Choung HK, Kim JH, Yu YS. Incidence and clinical features of ethambutol-induced optic neuropathy in Korea. J Neuroophthalmol 2008;28:269-77.
11. Chen SC, Lin MC, Sheu SJ. Incidence and prognostic factor of ethambutol-related optic neuropathy: 10-year experience in southern Taiwan. Kaohsiung J Med Sci 2015;31:358-62.
12. Kumar A, Sandramouli S, Verma L, Tewari HK, Khosla PK. Ocular ethambutol toxicity: Is it reversible? J Clin Neuroophthalmol 1993;13:15-7.
13. Woung LC, Jou JR, Liaw SL. Visual function in recovered ethambutol optic neuropathy. J Ocular Pharmacol Ther 1995;11:411–9.
14. Wang MY, Sadun AA. Drug-related mitochondrial optic neuropathies. J Neuroophthalmol 2013;33:172-8.
15. Grzybowski A, Zulsdorff M, Wilhelm H, Tonagel F. Toxic optic neuropathies. Acta Ophthamol 2015;93:402-10.
16. Yiannikas C, Walsh JC, McLeod G. Visual evoked potentials in the detection of subclinical optic toxic effects secondary to ethambutol. Arch Neurol 1983;40:645–8.
17. Srivastava AK, Goel UC, Bajaj S, Singh KJ, Dwivedi NC, Tandon MP. Visual evoked responses in ethambutol induced optic neuritis. J Assoc Physicians India 1997;45:847-9.
18. Menon V, Jain D, Saxena R, Sood R. Prospective evaluation of visual function for early detection of ethambutol toxicity. Br J Ophthalmol 2009;93:1251–4.
19. Kim KL, Park SP. Visual function test for early detection of ethambutol induced ocular toxicity at the subclinical level. Cutan Ocul Toxicol 2016;35:228–32.
20. Osaguona VB, Sharpe JA, Awaji SA, Farb RI, Sundaram AN. Optic chiasm involvement on MRI with ethambutol-induced bitemporal hemianopia. J Neuroophthalmol 2014;34:155-8.
21. Geyer HL, Herskovitz S, Slamovits TL, Schaumburg HH. Optochiasmatic and peripheral neuropathy due to ethambutol overtreatment. J Neuroophthalmol 2014;34:257-8.
22. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther 1997;13:473–7.
23. Chung H, Yoon YH, Hwang JJ, Cho KS, Koh JY, Kim JG. Ethambutol-induced toxicity is mediated by zinc and lysosomal membrane permeabilization in cultured retinal cells. Toxicol Appl Pharmacol 2009;235:163-70.
24. Kozak SF, Inderlied CB, Hsu HY, Heller KB, Sadun AA. The role of copper on ethambutol's antimicrobial action and implications for ethambutol-induced optic neuropathy. Diagn Microbiol Infect Dis 1998;30:83-7.
25. De Palma P, Franco F, Bragliani G, Michetti L, Marescotti A, Pirazzoli G, et al. The incidence of optic neuropathy in 84 patients treated with ethambutol. Metab Pediatr Syst Ophthalmol 1989;12:80-2.