

# Natural Course and Prognostic Factors of Ethambutol Toxic Optic Neuropathy

Ye Ji Kim

Yonsei University

Soo Hyun Lim

Kim's Eye Hospital

Ungsoo Kim (✉ [ungsookim@kimeye.com](mailto:ungsookim@kimeye.com))

Kim's Eye Hospital <https://orcid.org/0000-0003-2373-6240>

---

## Research article

**Keywords:** Ethambutol, Tuberculosis, Toxic optic neuropathy

**Posted Date:** October 26th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-76098/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** To investigate the natural course and prognostic factors of ethambutol toxic optic neuropathy (ETON).

**Methods:** Medical charts of 87 patients diagnosed with ETON were reviewed retrospectively, and the visual acuity and history of ethambutol medication were analyzed. Based on the final visual acuity, patients were divided into two groups: recovery and no-recovery groups. We investigated the prognostic factors, including the sex, age, duration of medication, initial visual acuity, and systemic diseases (diabetes mellitus, hypertension, renal disorders, etc.).

**Results:** In this study, 37 men and 50 women, with ages ranging from 22 to 91 years, were included. Although a poor initial visual acuity was noted in the old patients, a short duration of medication had a weak negative correlation with the initial visual acuity.

Follow-up of over 1 year could be performed for 28 out of 87 patients, including nine men and 19 women, with a mean age of  $70.0 \pm 8.2$  years. Ten eyes of seven (25%) patients, including three men and four women, did not recover vision after discontinuation of ethambutol. Patients were significantly older in the no-recovery group than in the recovery group ( $73.9 \pm 8.3$  and  $68.7 \pm 8.1$  years, respectively). The poor initial visual acuity and presence of systemic diseases affected the prognosis of ETON.

**Conclusion:** Three-fourth of patients with ETON had visual recovery after discontinuation of ethambutol. High-risk patients with poor prognostic factors, including old age, presence of systemic diseases, and poor initial visual acuity, should be screened in early stages of ETON.

## Introduction

Tuberculosis is a serious infectious disease worldwide, and the elderly population is particularly at a high risk.<sup>1,2</sup> Although ethambutol (EMB) hydrochloride is the first-line agent for treating tuberculosis, it has been associated with side effects.<sup>3</sup> Among these side effects, EMB toxic optic neuropathy (ETON) commonly occurs during the course of the medication.<sup>4</sup> However, only a few studies have investigated the natural course of ETON or response to discontinuation of EMB hydrochloride.<sup>5,6</sup> Chen et al. analyzed 16 patients with ETON and reported that 50% of them had visual impairment without recovery, with only the younger patients showing a favorable outcome.<sup>7</sup> However, another Korean study analyzed 13 patients with ETON and reported that only one-third of them had visual improvement after discontinuation. Therefore, the aim of this study was to analyze a large number of patients with ETON in terms of visual recovery in a follow-up period of over 1 year after discontinuation of EMB hydrochloride, focusing on the prognostic factors of ETON.

## Methods

This study was a retrospective review of the medical records of patients diagnosed with ETON at Kim's Eye Hospital from May 2008 to June 2018 for the analysis of bilateral visual loss after EMB medication. The study protocol was approved by the Institutional Review Board of Kim's Eye Hospital, and the study was conducted in accordance with the tenets of the Declaration of Helsinki. In order to analyze the recovery of visual function after discontinuation of the medication, patients with a history of optic neuropathy or ocular disorders that could induce progressive visual loss, such as age-related macular degeneration, dense cataract, and retinitis pigmentosa, were excluded. Furthermore, patients who underwent ocular surgery during the follow-up period were excluded.

We reviewed the visual acuity at the first and final visits and details of the EMB administration, including the duration and dosage. By comparing the final and initial visual acuities, the no-recovery group comprised patients with worsening or no improvement of visual acuity. We analyzed prognostic factors, including the sex, age, duration of medication, initial visual acuity, and systemic diseases (diabetes mellitus, hypertension, renal disorders, etc.).

Data were analyzed using SPSS, version 24.0 (IBM Corporation, Armonk, NY, USA), for Windows (Corporation, Redmond, WA, USA). Spearman's correlation coefficient was used to analyze correlations. Differences between the groups were investigated with the Mann–Whitney U and chi-square tests. Statistical significance was set at  $p < 0.05$ .

## Results

A total of 87 patients, including 37 men and 50 women, were enrolled in this study. The mean patient age was 66.9 years (range: 22 to 91 years). The dosage information was acquired for 21 patients, and the mean EMB dosage was 14.5 mg/kg/day (range: 13.3 to 15.0 mg/kg/day). The duration of medication before the onset of ETON was acquired for 72 patients, and the mean duration was  $5.97 \pm 3.16$  months. Although a poor initial visual acuity was noted in the old patients, a short duration of medication had a weak negative correlation with the initial visual acuity (Fig. 1). The initial visual acuity did not differ between the sexes (men,  $1.37 \pm 0.40$ ; women,  $1.48 \pm 0.65$ ,  $p = 0.47$ )

Follow-up of over 1 year could be performed for 28 out of 87 patients, including nine men and 19 women, with a mean age of  $70 \pm 8.2$  years. Of the 28 patients, ten eyes of seven patients did not recover vision after discontinuation of EMB (Fig. 2). The final visual acuity was lower compared to the initial visual acuity in three of 56 (5.4%) eyes (two men; mean age: 69.5 years). The visual acuity in the remaining seven eyes recovered after discontinuation of EMB (one man and four women; mean age: 71.6 years). Patients were significantly older in the no-recovery group than in the recovery group ( $73.9 \pm 8.3$  and  $68.7 \pm 8.1$  years, respectively). The poor initial visual acuity and presence of systemic diseases affected the prognosis of ETON (Table 1). The visual acuity recovered up to 0.8 on a decimal scale in 18 eyes of nine patients. All patients in the no-recovery group had a visual acuity worse than or equal to 0.1 on a decimal scale (Table 2). Gender difference was not found in the two groups (6 men and 15 women in the recovery group and 3 men and 4 women in the no-recovery group,  $p = .058$ )

Table 1  
Demographics of patients with ethambutol toxic optic neuropathy

	Recovery group	No-recovery group	P-value
Number of patients	21 (75%)	7 (25%)	-
Sex ratio (men:women)	6:15	3:4	.058*
Mean age of onset (years)	68.7 ± 8.1	73.9 ± 8.3	.013 <sup>¶</sup>
Initial VA (logMAR)	1.04 ± 0.51	1.61 ± 0.84	.003 <sup>¶</sup>
Systemic disorders	0.6	1.0	.025 <sup>¶</sup>
Duration of medication (months)	6.83 ± 5.09	5.40 ± 2.88	.643

VA, visual acuity; logMAR, logarithm of the minimum angle of resolution; \*Chi-square test,  $p = 0.058$ ; <sup>¶</sup>Mann-Whitney U test,  $p = 0.167$

Table 2  
Characteristics of patients in the no-recovery group

Age (years)/sex	Visual acuity at the first visit (Rt. eye/Lt. eye)	Visual acuity at the last visit (Rt. eye/Lt. eye)	Duration of medication (months)	Ethambutol dose (mg)	Systemic diseases or other medications
70'S-80'S/M	0.06/0.15	0.1/0.1	5	800	None
60'S-70'S/M	0.02/0.04	FC/FC	3	800	DM, HTN
70'S-80'S /F	0.06/0.06	0.06/0.06	2	-	DM, HTN
70'S-80'S /F	FC/0.02	FC/0.5	3	800	None
60'S-70'S/M	0.1/0.3	0.3/0.3	3	800	DM, renal failure
70'S-80'S /F	0.1/CF	0.1/0.02	6	800	Anti-depressants
80'S-90'S /F	CF/CF	CF/CF	10	-	None

Visual acuity is on a decimal scale. DM; diabetes mellitus, HTN; hypertension.

## Discussion

In the present study, 75% of patients with ETON had visual recovery after discontinuation of EMB, and old age, presence of systemic diseases, and a poor initial visual acuity were indicators of poor prognosis of ETON. The recovery rate was slightly higher in this study compared to previous studies (30–64%).<sup>3, 5, 7, 8</sup> This could be attributed to the different definitions of visual improvement used. In a previous study, although the visual acuity improved in some patients, other visual functions, including color vision, visual field, and electrophysiology, showed dysfunctions.<sup>9</sup>

The occurrence of ETON depends on the dosage of EMB<sup>10, 11</sup> and can also be induced by a relatively low dosage (10 mg/kg/day). We could not analyze the effects of dosage of EMB because the number of patients whose medical records had detailed information on the dosage was too small to draw meaningful results. However, the toxic dosage of EMB can be estimated considering that an initial dosage of 15 mg/kg/day is most widely used in Korea and that the average dosage of 14.5 mg/kg/day was used in this study. The mean interval between the start of medication and the onset of ETON was 3 to 5 months in a previous study<sup>12</sup> and  $5.97 \pm 3.16$  months in this study, showing similar results. The duration of medication did not affect the recovery from ETON. In addition, the initial visual acuity was worse in patients with a long duration of medication than in those with a short duration of medication, as previously reported in a Taiwanese study.<sup>7</sup> Therefore, further investigations of the correlation between the duration of medication and the severity of visual loss are required.

Several other risk factors, such as the age, sex, initial visual acuity, smoking habit, alcohol consumption, and presence of systemic diseases, including renal failure, have been associated with ETON.<sup>13, 14</sup> In the present study, old patients had a poor initial visual acuity and worse prognosis of ETON. Although the correlation between patient age and occurrence of ETON is debated,<sup>7, 15</sup> the positive correlation in this study could be attributed to the decline in renal function with age.<sup>16</sup> The presence of systemic diseases can affect not only the occurrence of ETON but also the deterioration of visual acuity.<sup>17</sup> Women showed a tendency for favorable visual outcome but without statistical significance. In Leber's hereditary optic neuropathy, which is a mitochondrial disorder,<sup>18</sup> male predominance is a unique feature, possibly attributable to the neuroprotective effect of the higher estrogen levels in women.<sup>19</sup> Among systemic diseases, we analyzed hypertension, diabetes mellitus, and renal disorders, and their presence affected the visual recovery, consistent with previous studies.<sup>7, 14</sup>

The exact mechanism underlying the occurrence of ETON after EMB administration is unclear, and several pathways have been suggested. First, EMB is particularly toxic to the retinal ganglion cells through the mechanism of glutamate excitotoxicity.<sup>20, 21</sup> Second, it is a zinc-chelating agent, which affects caspase-3 and caspase-6 pathways.<sup>22</sup> If the exact mechanism is identified, the association between prognostic factors and EMB could be better understood.

The present study had some limitations. First, only 28 out of 87 patients were followed-up for over 1 year, and this bias may have affected the recovery rate. Second, we could not evaluate the exact dosage administered to each patient, and the cumulative dosage of medication may have affected the visual

prognosis. Nevertheless, we can assume that other factors, such as patient age and presence of systemic diseases, are associated with ETON. Moreover, the recovery rate, which the present study aimed to investigate, could serve as reference for clinicians.

## Conclusions

Visual recovery after discontinuation of EMB is favorable. Furthermore, multiple patient factors, including the old age, poor initial visual acuity, and systemic diseases, should be considered during EMB administration to predict the recovery from ETON.

## Abbreviations

ETON  
ethambutol toxic optic neuropathy  
EMB  
ethambutol

## Declarations

### - Ethics approval and consent to participate

not applicable

### - Consent to publish

not applicable

### - Availability of data and materials

Supplement data is attached.

### - Competing interests

None

### - Funding

None

### - Authors' Contributions

All authors are involved in the design and concept of the study. YJ Kim and SH Lim collected and analyzed data. YJ Kim wrote primary manuscript and US Kim supervised the manuscript.

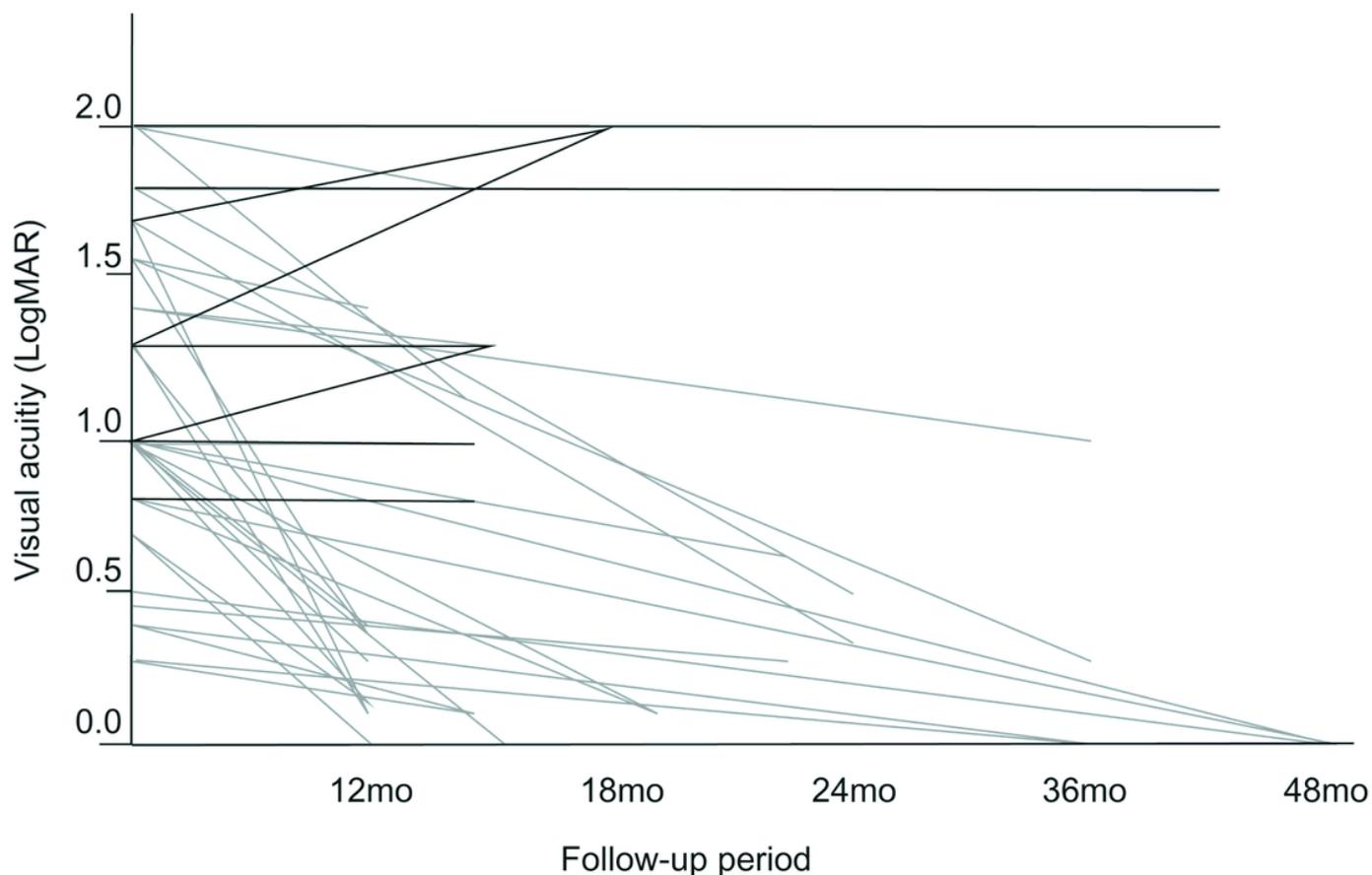
### - Acknowledgements

## References

1. Kim JH, Yim JJ. Achievements in and Challenges of Tuberculosis Control in South Korea. *Emerg Infect Dis*. 2015;21(11):1913–20.
2. Sadun AA, Wang MY. Ethambutol optic neuropathy: how we can prevent 100,000 new cases of blindness each year. *J Neuroophthalmol*. 2008;28(4):265–8.
3. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol optic neuropathy. *Curr Opin Ophthalmol*. 2017;28(6):545–51.
4. Yang HK, Park MJ, Lee JH, Lee CT, Park JS, Hwang JM. Incidence of toxic optic neuropathy with low-dose ethambutol. *Int J Tuberc Lung Dis*. 2016;20(2):261–4.
5. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. *J Ocul Pharmacol Ther*. 1997;13(5):473–7.
6. Kumar A, Sandramouli S, Verma L, Tewari HK, Khosla PK. Ocular ethambutol toxicity: is it reversible? *J Clin Neuroophthalmol*. 1993;13(1):15–7.
7. 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(7):358–62.
8. 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(4):269–77.
9. Nasemann J, Zrenner E, Riedel KG. Recovery after severe ethambutol intoxication—psychophysical and electrophysiological correlations. *Doc Ophthalmol*. 1989;71(3):279–92.
10. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax*. 1986;41(10):737–9.
11. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. *Ann N Y Acad Sci*. 1966;135(2):904–9.
12. Chan RY, Kwok AK. Ocular toxicity of ethambutol. *Hong Kong Med J*. 2006;12(1):56–60.
13. Chuenkongkaew W, Samsen P, Thanasombatsakul N. Ethambutol and optic neuropathy. *J Med Assoc Thai*. 2003;86(7):622–5.
14. Talbert Estlin KA, Sadun AA. Risk factors for ethambutol optic toxicity. *Int Ophthalmol*. 2010;30(1):63–72.
15. Chen HY, Lai SW, Muo CH, Chen PC, Wang IJ. Ethambutol-induced optic neuropathy: a nationwide population-based study from Taiwan. *Br J Ophthalmol*. 2012;96(11):1368–71.
16. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc*. 1985;33(4):278–85.
17. Grzybowski A, Zulsdorff M, Wilhelm H, Tonagel F. Toxic optic neuropathies: an updated review. *Acta Ophthalmol*. 2015;93(5):402–10.

18. Jurkute N, Yu-Wai-Man P. Leber hereditary optic neuropathy: bridging the translational gap. *Curr Opin Ophthalmol*. 2017;28(5):403–9.
19. Prokai-Tatrai K, Xin H, Nguyen V, Szarka S, Blazics B, Prokai L, et al. 17beta-estradiol eye drops protect the retinal ganglion cell layer and preserve visual function in an in vivo model of glaucoma. *Mol Pharm*. 2013;10(8):3253–61.
20. Yoon YH, Jung KH, Sadun AA, Shin HC, Koh JY. Ethambutol-induced vacuolar changes and neuronal loss in rat retinal cell culture: mediation by endogenous zinc. *Toxicol Appl Pharmacol*. 2000;162(2):107–14.
21. Heng JE, Vorwerk CK, Lessell E, Zurakowski D, Levin LA, Dreyer EB. Ethambutol is toxic to retinal ganglion cells via an excitotoxic pathway. *Invest Ophthalmol Vis Sci*. 1999;40(1):190–6.
22. Shindler KS, Zurakowski D, Dreyer EB. Caspase inhibitors block zinc-chelator induced death of retinal ganglion cells. *Neuroreport*. 2000;11(10):2299–302.

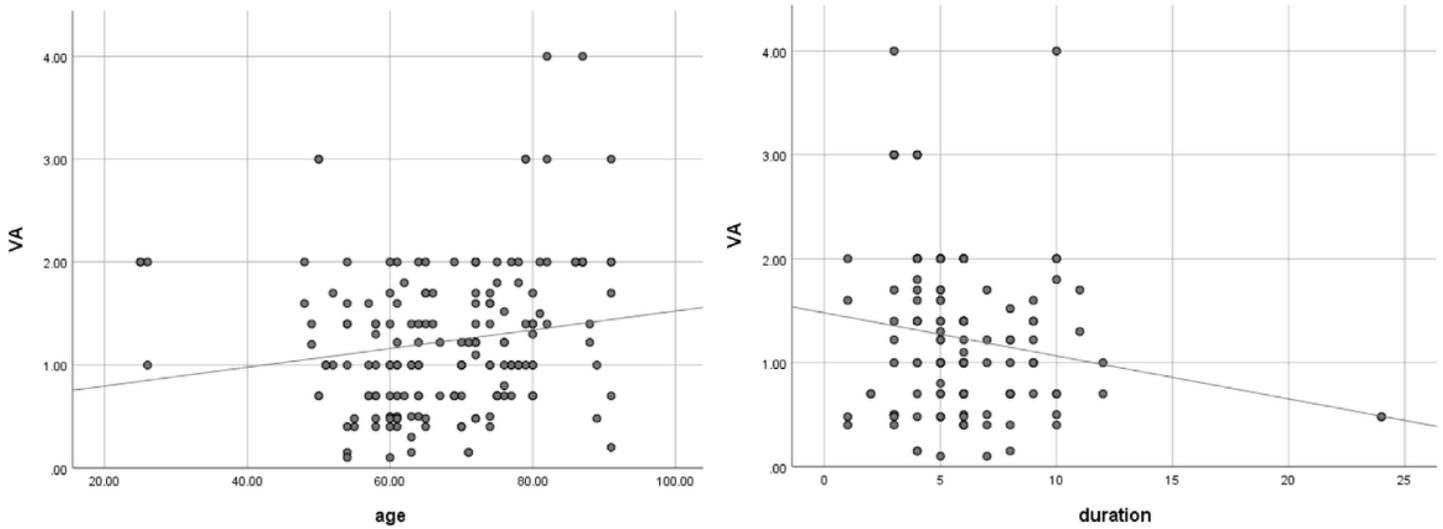
## Figures



**Figure 1**

Correlation between the initial visual acuity and prognostic factors, including patient age and duration of medication. The initial visual acuity is worse in old patients ( $r = 0.213$ ,  $p = 0.005$ ) and patients with a

short duration of medication ( $r = -.180, p = 0.034$ ).



**Figure 2**

Changes in visual acuity over time. The dense black lines indicate the no-recovery group, and thin black lines indicate the recovery group.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CRFBMC.xlsx](#)