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ORIGINAL ARTICLE

# Incidence and prognostic factor of ethambutol-related optic neuropathy: 10-year experience in southern Taiwan

**Shih-Chou Chen** [a,*], **Muh-Chiou Lin** [a], **Shwu-Jiuan Sheu** [a,b]

[a] *Department of Ophthalmology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*

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**Abstract** To investigate the incidence and prognostic factors of ethambutol-related optic neuropathy (EON) in one medical center of southern Taiwan, a retrospective chart review study with 4803 newly diagnosed tuberculosis cases from January 2002 to July 2011 at one medical center hospital in southern Taiwan were reviewed. Of these patients, 1004 had ophthalmic records. Sixty-two cases (1.29%) experienced visual impairment and were diagnosed as EON with mean visual acuity of 0.86 ± 0.69 by logMAR. Sixteen of the 62 patients had a follow-up time > 6 months. Of these, eight patients (50%) showed visual improvement (an increase in visual acuity of ≥ 2 Snellen lines) after ethambutol was discontinued. Another eight patients (50%) showed no visual improvement. We analyzed multiple factors between the patients with and without visual improvement by logistic regression, including body weight, daily dose of ethambutol, duration of ethambutol use, cumulative dose of ethambutol, renal function, underlying disease of diabetes mellitus, hypertension, and initial visual acuity showed no statistically significant difference. In conclusion, the incidence of EON was 1.29%. Half of the patients showed visual improvement after discontinuation of ethambutol, and no obvious prognostic factors were found to facilitate the vision recovery. Ethambutol should be discontinued as soon as EON is suspected.


Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Ophthalmology, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung, 813, Taiwan.
*E-mail address:* achoes@vghks.gov.tw (S.-C. Chen).

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## Introduction

Tuberculosis is one of the most important systemic infections throughout the world, and it is caused by *Mycobacterium tuberculosis* [1]. Tuberculosis should be treated with the combination of antituberculous drugs. Ethambutol has been used to treat tuberculosis since the 1960s, but the related visual impairment was recognized soon after its introduction [2]. Ethambutol-related optic neuropathy (EON) has become an established ocular complication and may lead to permanent visual loss. There have been several studies regarding the incidence of EON in different countries. The incidence was ~1% and correlated with dosage [3–5]. However, no literature was available in southern Taiwan. The purpose of this study is to investigate the incidence and clinical features of EON in one medical center of southern Taiwan.

## Methods

We conducted a retrospective chart review of patients diagnosed and filed as tuberculosis in the Infection Control Center from January 2002 to July 2011 at our hospital. Patients who experienced visual impairment after the initiation of ethambutol use and diagnosed as EON based on ophthalmic records were collected. The visual symptoms and signs included decreased visual acuity, impaired color vision by Ishihara color plate, or abnormal results of visual field and/or flash and pattern visual evoked potential examinations. Patients with vision impairment related to other ophthalmologic problems such as cataract, retinal disease, glaucoma, and other cause of optic neuropathy were excluded. Data variables included age, sex, medical history, date of diagnosis, treatment, visual acuity, color vision, slit lamp biomicroscopy, fundus and other ophthalmic examination if eligible. Patients diagnosed as EON with a follow-up time of $>$ 6 months were further investigated for surveying the prognostic factor of EON.

SPSS Statistics software version 17 (SPSS Inc., Chicago, IL, USA) was used for analysis of results. Descriptive statistics were expressed as mean, with standard deviation. Means of normally distributed variables were compared with logistic regression analysis. Odds ratios were also calculated. The *p* value or 95% confidence interval was calculated as appropriate. For statistical analysis, decimal fractions of visual acuity were converted to a logarithmic scale (the logarithm of the minimal angle of resolution). The Institutional Review Board and Ethics Committee of Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan approved this study, which adhered to the tenets of the Declaration of Helsinki; patient consent was not required.

## Results

In the retrospective chart review, 4803 cases were diagnosed and filed as tuberculosis in the Infection Control Center of Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan from January 2002 to July 2011, of whom 1004 had ophthalmic records. Sixty-two patients (1.29%) experienced visual impairment and were diagnosed as EON. Mean age of affected patients was 70.02 ± 14.26 years (range, 27–90 years). Forty-one were male and 21 female. Mean body weight was 56.59 ± 11.79 kg (range. 30.7–80.9 kg). Mean ethambutol daily dose was 16.06 ± 4.36 mg/kg (range, 6.3–32.6 mg/kg). Average duration of ethambutol use was 5.94 ± 4.06 months (range, 1–21 months). Mean ethambutol cumulative dose was 2820.02 ± 2157.39 mg/kg (range, 270–10,749 mg/kg). Average follow-up time was 5.87 ± 11.61 months (range, 0–60 months; Table 1). Twenty-one of the 62 patients had visual field examinations; seven showed constricted, seven showed general decrease, and five showed paracentral scotoma. In the nine patients who had flash and pattern visual evoked potentials tests, delayed latency was seen in five patients and poor waveform was seen in four.

Of the above 62 patients, 16 were followed-up in our ophthalmic clinic for $>$ 6 months. Fifteen patients suffered from primary pulmonary tuberculosis, and one patient suffered from primary bone marrow tuberculosis. Their ethambutol dose ranged from 400 mg/d to 1600 mg/d. Eight patients (50%) showed visual improvement (an increase in visual acuity of $\geq$ 2 Snellen lines) after ethambutol was discontinued; another eight patients (50%) showed no visual improvement after discontinuation of ethambutol. The detailed clinical presentations of the 16 patients diagnosed as EON with a follow-up time of $>$ 6 months are listed in Table 2.

The mean age of the 16 patients was 76.75 ± 7.21 years (range, 59–85 years). Their mean body weight was 57.91 ± 12.29 kg (range, 35.0–80.0 kg). Mean ethambutol daily dose was 16.37 ± 4.46 mg/kg (range, 7.3–24.2 mg/kg), average duration of ethambutol use was 7.56 ± 4.88 months (range, 1–21 months), and mean ethambutol cumulative dose was 3479.46 ± 2189.16 mg/kg (range, 615–9450 mg/kg). Mean glomerular filtration rate was 46.38 ± 19.19 mL/min (range, 5.5–80.0 mL/min). Average follow-up time was 19.44 ± 16.65 months (range, 6–60 months). The visual acuity improved from 0.84 ± 0.39 to 0.28 ± 0.21 by logMAR in the visual improved group and only changed from 1.07 ± 0.87 to 0.96 ± 0.76 by logMAR in the nonimproved group (Table 3).

Multiple factors including age, sex, body weight, ethambutol daily dose, ethambutol duration, ethambutol cumulative dose, glomerular infiltration rate, underlying disease of diabetes, hypertension, and initial visual acuity

**Table 1** Characteristics of the 62 patients with ethambutol-related optic neuropathy.

| Variables | *N* | Mean ± SD |
|---|---|---|
| Age (y) | 62 | 70.02 ± 14.26 |
| Weight (kg) | 62 | 56.59 ± 11.79 |
| EMB daily dose (mg/d) | 62 | 16.06 ± 4.36 |
| EMB duration (mo) | 62 | 5.94 ± 4.06 |
| EMB cumulative dose (mg/kg) | 62 | 2820.02 ± 2157.39 |
| Initial VA logMAR | 124 (eyes) | 0.86 ± 0.69 |
| Initial color (Ishihara color test) | 112 (eyes) | 7.23 ± 8.53 |
| Follow-up time (mo) | 62 | 5.87 ± 11.61 |

**Table 2** Clinical presentation of the 16 patients diagnosed with ethambutol-related optic neuropathy with a follow-up time of more than 6 months.

| Case | Sex | Age (y) | Weight (kg) | Tuberculosis involved organ | EMB dose (mg/kg) | EMB daily dose (mg/kg) | EMB duration (mo) | EMB cumulative dose (mg/kg) | Glomerular filtration rate (mL/min) | Follow-up time (mo) | Systemic disease | OD | | | | OS | | | | Improvement |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Initial VA | Final VA | Initial color | Final color | Initial VA | Final VA | Initial color | Final color | |
| 1 | M | 82 | 52.4 | Lung | 800 | 15.3 | 6 | 2748 | 52.8 | 13 | DM, colon cancer | 6/20 | 6/20 | 21/21 | — | 6/15 | 6/20 | 21/21 | — | — |
| 2 | M | 85 | 68.0 | Lung | 800 | 11.8 | 13 | 4588 | 43.3 | 46 | DM, HTN, Sicca syndrome | 6/20 | 6/6 | 1/21 | 21/21 | 6/60 | 6/8.6 | 0/21 | 7/21 | OU |
| 3 | M | 84 | 58.5 | Lung | 1200 | 20.5 | 1 | 615 | 16.9 | 60 | HTN | 6/12 | 6/15 | 2/21 | — | 6/12 | 6/20 | 2/21 | — | — |
| 4 | F | 76 | 42.0 | Lung | 800 | 19.0 | 8 | 4571 | 63.5 | 17 | Colon cancer | 6/60 | 3/60 | — | — | 1/60 | 4/60 | — | — | — |
| 5 | M | 77 | 58.0 | Lung | 1200 | 20.7 | 1 | 621 | 63.4 | 32 | — | 6/30 | 6/30 | 12/21 | 6/21 | 6/30 | 6/30 | 13/21 | 15/21 | — |
| 6 | M | 82 | 79.5 | Lung | 1200 | 15.1 | 5 | 2264 | 42.7 | 9 | Colon cancer | 6/30 | 6/7.5 | 0/21 | 21/21 | 3/60 | 6/8.6 | 1/21 | 21/21 | OU |
| 7 | M | 84 | 52.5 | Lung | 800 | 15.2 | 12 | 5486 | 45.4 | 43 | — | 6/30 | 6/12 | 9/21 | 20/21 | 6/30 | 6/12 | 11/21 | 19/21 | OU |
| 8 | F | 76 | 55.1 | Bone marrow | 400 | 7.3 | 6 | 1307 | 5.5 | 10 | ESRD | 6/30 | 6/8.6 | 1/21 | 19/21 | 6/60 | 6/12 | 1/21 | 19/21 | OU |
| 9 | M | 67 | 63.1 | Lung | 800 | 12.7 | 6 | 2282 | 80.0 | 17 | Polymyositis | 6/60 | 6/30 | 7/21 | — | 4/60 | 6/20 | 8/21 | — | OS |
| 10 | M | 78 | 64.4 | Lung | 800 | 12.4 | 9 | 3354 | 34.7 | 6 | DM, HTN, CAD | 4/60 | 6/60 | 0/21 | 1/21 | CF | 1/60 | 0/21 | 0/21 | — |
| 11 | M | 83 | 45.0 | Lung | 800 | 17.8 | 9 | 4800 | 32.4 | 15 | — | CF | CF | 0/21 | 0/21 | CF | CF | 0/21 | 0/21 | — |
| 12 | M | 72 | 58.0 | Lung | 800 | 13.8 | 8 | 3310 | 32.2 | 7 | — | 6/60 | 6/60 | 5/21 | 5/21 | 6/60 | 6/30 | 5/21 | 5/21 | — |
| 13 | F | 77 | 35.0 | Lung | 800 | 22.9 | 7 | 4800 | 52.1 | 6 | — | 6/12 | 6/20 | 18/21 | 21/21 | 6/7.5 | 6/8.6 | 21/21 | 21/21 | — |
| 14 | M | 78 | 49.5 | Lung | 1200 | 24.2 | 3 | 2182 | 53.3 | 15 | HTN | 5/60 | 6/15 | 0/21 | 1/21 | 1/60 | 6/30 | 0/21 | 1/21 | OU |
| 15 | M | 68 | 65.6 | Lung | 1200 | 18.3 | 6 | 3293 | 54.7 | 6 | — | 6/15 | 6/7.5 | 5/21 | 21/21 | 6/15 | 6/7.5 | 5/21 | 21/21 | OU |
| 16 | M | 59 | 80.0 | Lung | 1200 | 15.0 | 21 | 9450 | 69.2 | 9 | DM, HTN | 6/30 | 6/15 | 2/21 | — | 6/10 | 6/7.5 | 3/21 | — | OU |

OD = right eye; OS = left eye; OU = both eyes; VA = visual acuity; CF = counting fingers; DM = diabetes mellitus; HTN = hypertension; CAD = coronary artery disease.

**Table 3** Characteristics of the 16 ethambutol-related optic neuropathy patients with or without visual improvement for a follow-up time of more than 6 months.

| | Total ($n = 16$) | Visual improvement ($n = 8$) | No visual improvement ($n = 8$) |
|---|---|---|---|
| Age (y) | 76.75 ± 7.21 | 74.88 ± 9.33 | 78.63 ± 4.07 |
| Sex (male/female) | 13/3 | 7/1 | 6/2 |
| Weight (kg) | 57.91 ± 12.29 | 64.16 ± 11.57 | 51.66 ± 10.04 |
| EMB daily dose (mg/kg) | 16.37 ± 4.46 | 14.95 ± 4.96 | 17.80 ± 3.67 |
| EMB duration (mo) | 7.56 ± 4.88 | 9.00 ± 5.95 | 6.13 ± 3.31 |
| EMB cumulative dose (mg/kg) | 3479.46 ± 2189.16 | 3856.50 ± 2648.83 | 3102.38 ± 1711.18 |
| Glomerular filtration rate (mL/min) | 46.38 ± 19.19 | 49.26 ± 22.03 | 43.50 ± 16.87 |
| Diabetes mellitus | 4 | 2 | 2 |
| Hypertension | 5 | 3 | 2 |
| Follow-up time (mo) | 19.44 ± 16.65 | 19.38 ± 15.92 | 19.50 ± 18.46 |
| Initial VA logMAR (32 eyes) | 0.95 ± 0.67 | 0.84 ± 0.39 | 1.07 ± 0.87 |
| Final VA logMAR (32 eyes) | 0.62 ± 0.65 | 0.28 ± 0.21 | 0.96 ± 0.76 |

EMB = ethambutol; VA = visual acuity.

were analyzed by logistic regression analysis. Between the visual improved group and nonimproved group, no statistically significant difference was found between the above factors (Table 4).

## Discussion

In our study, the incidence of EON was 1.29%. Compared with previous studies, a 1.5% incidence of EON was reported in a recent study from Korea [5], and earlier studies reported an incidence of around 1% [2,6,7]. Ezer et al [8] reported a meta-analysis searching Cochrane, Embase, and PubMed electronic databases from 1965 to February 2011 for studies regarding tuberculosis patients treated with ethambutol, any visual impairment occurred in 22.5/1000 persons receiving ethambutol at standard doses for up to 9 months, and permanent impairment in 2.3/1000 [8]. The result of our study was comparable to previous studies, but the actual incidence of EON might be underestimated. In the 4803 cases diagnosed and filed as tuberculosis, only 1004 patients had ophthalmic records. We believe that the incidence of EON should be much lower in the residual 3799 patients without ophthalmic records, but if any EON was overlooked among these patients, the accurate incidence of EON might be higher.

The visual function recovery after discontinuation of ethambutol was seen in eight of the 16 patients with a follow-up time of $>$ 6 months. The recovery rate was 50%. In previous studies, Kumar et al [9] described a series of seven consecutive patients with severe visual deficit due to ethambutol toxicity, only 42.2% (3 of the 7 patients) achieved a visual recovery of better than 20/200 after an average follow-up of 8.3 ± 2.1 months after stoppage of the drug [9]. Lim [3] described three cases of EON presented with bitemporal hemianopia, and only one case recovered visual function after stopping ethambutol use. Subsequent improvement was mild in another two cases. Tsai and Lee [10] described 10 consecutive patients with severe visual defects due to ethambutol toxicity. Five patients (50%) experienced visual improvement after 1—3 years follow-up, and the other five showed no recovery. Lee et al [5]

**Table 4** Analysis of possible factors contributing to visual improvement in ethambutol-related optic neuropathy patients with a follow-up time of more than 6 months (adjusted for age and sex).

| Variables | Adjusted odds ratio | 95% confidence interval | | $p$ |
|---|---|---|---|---|
| | | Lower | Upper | |
| Weight (kg) | 1.153 | 0.975 | 1.363 | 0.095 |
| EMB daily dose (mg/kg) | 0.851 | 0.655 | 1.105 | 0.226 |
| EMB duration (mo) | 1.166 | 0.853 | 1.596 | 0.336 |
| EMB cumulative dose (mg/kg) | 1.000 | 0.999 | 1.001 | 0.665 |
| Glomerular filtration rate (mL/min) | 0.999 | 0.936 | 1.066 | 0.969 |
| Diabetes mellitus | 0.739 | 0.059 | 9.260 | 0.815 |
| Hypertension | 0.284 | 0.028 | 2.839 | 0.284 |
| Initial VA logMAR | 0.544 | 0.088 | 3.354 | 0.512 |

$p < 0.05$ was considered to be significant.
EMB = ethambutol; VA = visual acuity.

reported a retrospective chart review study in Korea and only slightly less than one third of patients showed improvement in visual function after discontinuing ethambutol. Visual function recovery rate after discontinuation of ethambutol was comparable in our study to previous reports.

In this study, the mean ethambutol daily dose of patients developing EON was 16.06 ± 4.36 mg/kg, while previous study suggested an increased risk of EON if the daily dose of ethambutol was over 15 mg/kg [11]. In a recent nationwide population-based study about EON reported by Chen et al [12], age, hypertension, and renal diseases are risk factors for EON, but higher average daily dose was not correlated with an increased risk for EON in the Taiwanese population [12].

In the 16 patients with a follow-up time of > 6 months, eight showed visual improvement with visual acuity improved from 0.84 ± 0.39 to 0.28 ± 0.21 by logMAR, and eight showed no visual improvement with visual acuity only changed from 1.07 ± 0.87 to 0.96 ± 0.76 by logMAR. No statistically significant difference was found in the age, sex, body weight, ethambutol daily dose, ethambutol duration, ethambutol cumulative dose, renal function, underlying disease of diabetes mellitus, hypertension, and initial visual acuity between patients with visual improvement and nonimprovement.

In the report of Kumar et al [9], three patients achieved a visual recovery from seven consecutive patients with severe visual deficit due to ethambutol toxicity. There were no predisposing or risk factors to contribute toward the poor visual gain [9]. In another case series from Tsai et al [10], there were also no predisposing or risk factors to contribute to the poor visual gain after stoppage of ethambutol use. Regarding the reversibility of EON, no obvious prognostic factors were mentioned in previous reports. In our study, no obvious prognostic factor could be identified maybe due to the small sample size with only 16 cases included. The body weight of the visual improved group seemed to be heavier than the nonimproved group, but $p > 0.05$ remained ($p = 0.095$). Most of the patients with EON were elderly patients. Maybe among these elderly patients, the general nutrition status of heavier patients was better, leading to better visual improvement in EON after discontinuation of ethambutol use. It reminds us that in the treatment of tuberculosis with ethambutol, we should be very careful in the dose of ethambutol used in leaner patients.

The ethambutol daily dose is higher in the group of patients without visual improvement than the patients with visual improvement (17.80 ± 3.67 mg/d vs. 14.94 ± 4.96 mg/d; $p = 0.226$). Daily dose of visual improvement group was < 15 mg/kg, and daily dose of the nonimprovement group was > 15 mg/kg. Coincidently, previous study also suggested an increased risk of EON if the daily dose of ethambutol was > 15 mg/kg [11]. In the treatment course with ethambutol, the daily dose of ethambutol should be better controlled within no more than 15 mg/kg.

We also noted a trend that older patients show poorer visual recovery. The age is higher in the group of patients without visual improvement than the patients with visual improvement (78.63 ± 4.07 vs. 74.88 ± 9.32). We have to pay more attention in the monitoring of side effects of EON during the use of ethambutol in older patients.

## Conclusion

In this study, we estimated that the incidence of EON in tuberculosis patients receiving ethambutol treatment was at least 1.29%. The vision recovery rate after discontinuation of ethambutol was 50% at 6-month follow-up. Regarding the recovery of visual function in EON patients, no statistically significance was observed in the body weight, diabetes mellitus, hypertension, renal function, daily dose, duration, or cumulative dose of ethambutol use. There was a trend that lower body weight, age, and higher daily dose of ethambutol use were related to poorer visual recovery, but this was not significant. Since half of patients with EON suffered from irreversible loss of visual function, ethambutol should be discontinued promptly if EON was suspected to prevent further optic nerve damage.

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