

[CASE REPORT]

Drastically Progressive Ethambutol-induced Optic Neuropathy after Withdrawal of Ethambutol: A Case Report and Literature Review

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Abstract:

Ethambutol-induced optic neuropathy (EON) is a well-known complication, although low-dose ethambutol seldom causes EON. An 85-year-old man with non-tuberculous mycobacterial lung disease was taking antibiotics, including low-dose ethambutol. On day 85 of treatment, the diagnosis of EON was made. Despite prior discontinuation, his best corrected visual acuity drastically deteriorated from 20/17 (right eye) and 20/20 (left eye) to 20/330 (right eye) and 20/1,000 (left eye) within 3 weeks, and this symptom did not resolve. To our knowledge, there have been no reported cases with drastically progressing and irreversible EON even after the withdrawal of low-dose and short-term ethambutol.

Key words: ethambutol-induced optic neuropathy, non-tuberculosis mycobacterium, low dose ethambutol

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Introduction

Ethambutol-induced optic neuropathy (EON) is a well-known complication that is commonly seen during treatment with ethambutol. It was reported that 0.7-2.25% of patients on ethambutol experienced EON (1-3). The risk factors for EON are reportedly old age, an impaired renal function, and hypertension (3, 4). In addition, EON occurrence is dependent on the duration and dose of administration (5). In some reports, low-dose ethambutol (≤ 15 mg/kg) resulted in a low incidence rate of EON (2, 3). Furthermore, the damage is classically thought to be reversible after the discontinuation of the administration of ethambutol. Only a small number of cases of permanent damage to the visual function (2.3/1,000 persons treated; 95% confidence interval 0-6.1) were reported in a recent epidemiologic study (1), and it is rare for visual impairment to rapidly progress even after the discontinuation of ethambutol.

We herein report a case of EON that drastically pro-

gressed after the withdrawal of low-dose ethambutol and present a literature review.

Case Report

An 85-year-old man with progressive development of sputum and lung infiltration was referred to our hospital. He had a history of repeated treatment with clarithromycin or azithromycin for chronic lower respiratory tract infection. His oxygen saturation level was 99% on room air, and his body temperature was 36.6°C.

A laboratory examination revealed a white blood cell count of 7,400/mm³ with a neutrophil percentage of 65.9% and C-reactive protein level of 2.0 mg/dL. Chest X-ray and computed tomography revealed infiltrates in both lower lung fields (Fig. 1A, B). Previous sputum cultures found *Pseudomonas aeruginosa*, which was considered to be a colonizing bacteria, but no acid-fast bacteria were seen. Bronchoscopy was performed to obtain a lower respiratory tract specimen. Bacterial culture found *P. aeruginosa*; however, the smear

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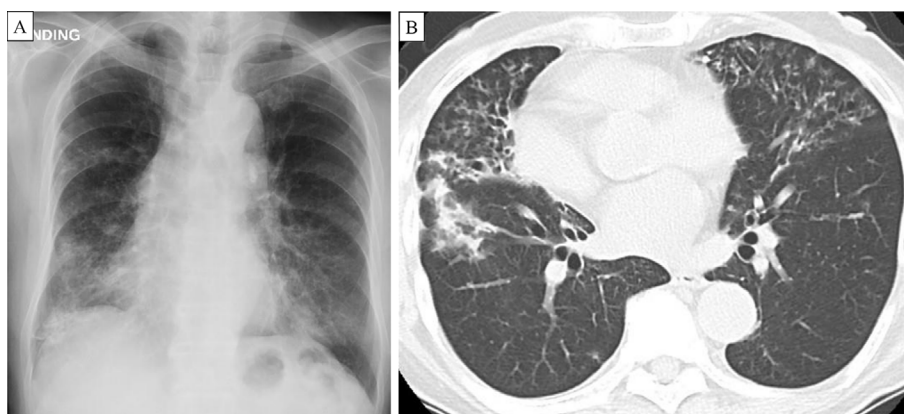


Figure 1. (A) Chest X-ray at the time of the patient's referral showing infiltrations in both lower lung fields. (B) Chest computed tomography at the time of the patient's referral showing bronchiectasis with infiltrations in the middle and lower lobes of the right lung and lower lobe of the left lung.

and polymerase chain reaction for *Mycobacterium tuberculosis*, *M. avium*, and *M. intracellulare* DNA isolated from the bronchial lavage fluid were negative.

Although the short-term administration of levofloxacin was effective, the complaint of sputum and lung infiltration persisted. Given that the *M. avium* complex-specific glycopeptidolipid core antigen antibody level was positive and the patient wished to receive some treatment, the administration of antibiotics (clarithromycin, 800 mg/day, rifampicin, 450 mg/day, and ethambutol, 750 mg/day) was initiated following the clinical diagnosis of non-tuberculous mycobacterial lung disease. His body weight was 62 kg, and his renal function was normal. After the initiation of antibiotics, the complaints of sputum and lung infiltration were partially improved; therefore, the treatment was continued. Given that he had a private ophthalmologist, we left the monitoring of visual impairment to him. His initial ophthalmologic check was normal, and his best corrected visual acuity was 20/20 (right eye) and 20/17 (left eye).

On day 75 of treatment, he experienced blurred vision. Since his private ophthalmologist had not recommended the discontinuation of ethambutol, we referred him to our attending ophthalmologist due to suspicions of EON on day 85 of treatment. His best corrected visual acuity was 20/17 (right eye) and 20/20 (left eye), and his intraocular pressure was normal. The pupils were reactive in both eyes with no relative afferent pupillary defect. The slit lamp microscope examination results were normal. A fundoscopic examination showed no abnormalities. Automated perimetry showed mild enlargement of the blind spot. Optical coherence tomography showed that the retinal nerve fiber layer thickness was within normal range. Based on these ocular examination findings and the clinical course of the disease, a diagnosis of EON was reached at.

Given that he had stopped taking ethambutol the day before the ophthalmology consult by his personal judgement, we approved the discontinuation of the drug. Thereafter, however, his best corrected visual acuity drastically worsened to 20/330 (right eye) and 20/1,000 (left eye) within 3

weeks (Fig. 2). Brain magnetic resonance imaging showed high-density areas in the margins of both retrobulbar optic nerves on fat-suppressed T2-weighted imaging without atrophy of the optic nerve, which suggested optic perineuritis, and the contribution of other diseases was not suggested (Fig. 3). Mecobalamin was administered, but the visual acuity had hardly improved at four months after withdrawal (Fig. 2).

Discussion

We reported a case of drastically progressive EON even after the withdrawal of ethambutol. In this case, although the patient was advanced in age, his renal function was normal, there was no history of hypertension, the dose of ethambutol was low (12 mg/kg), the duration of administration was short (2.5 months), and ethambutol was discontinued properly before the apparent visual impairment started; however, catastrophic visual impairment occurred.

The exact pathophysiologic mechanism underlying EON is unknown, although it may be caused by disrupted oxidative phosphorylation secondary to decreased available copper in human mitochondria or from inhibited lysosomal activation due to the chelation of zinc (6). There have been reports stating that EON is a dose- and time-dependent adverse effect. The incidence rate was reported to be <1%, 3%, 5-6%, and 18-33% at doses of ≤ 15 , 20, 25, and >35 mg/kg per day of ethambutol, respectively (2, 7-9). In the present case, a low dose of ethambutol was administered. However, in a Japanese national survey, 12 out of 23 EON cases (52.2%) were caused by low-dose ethambutol (<15 mg/kg), and about 10% of EON cases occurred within 2 months of the start of administration (10). There is no safe dose at which EON can be avoided, and therefore we may need to monitor for EON even in cases of low-dose ethambutol, especially in Japanese patients. Although most previous reports concerned patients with tuberculosis, Griffith et al. reported an incidence rate of EON of 6% (8 of 139 patients) for patients with *M. avium* complex (MAC) lung dis-

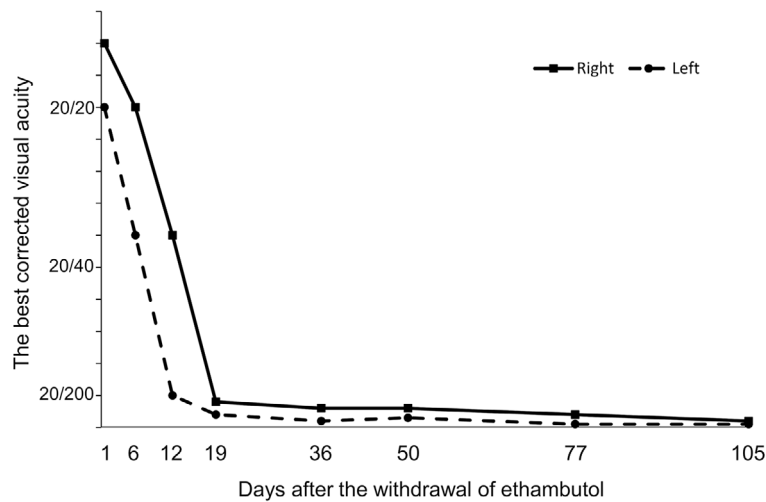


Figure 2. Clinical course of the best corrected visual acuity after the withdrawal of ethambutol. The continuous line with squares represents the best corrected visual acuity in right eye, and the dashed line with circles represents the best corrected visual acuity in the left eye.

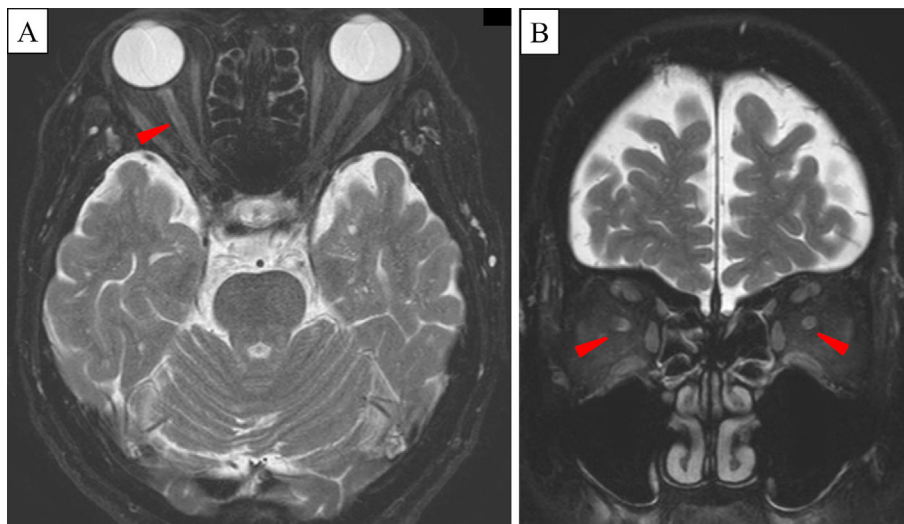


Figure 3. Brain magnetic resonance imaging showing high-density areas in the margins of both retrobulbar optic nerves on fat-suppressed T2-weighted imaging without atrophy of the optic nerve, which suggests optic perineuritis (with red arrowheads). (A) Horizontal section. (B) Coronal section.

ease, and all returned to their baseline ocular statuses after the discontinuation of ethambutol (11). In addition, a recent clinical practice guideline conditionally recommended a three-times-per-week macrolide-based regimen rather than a daily macrolide-based regimen in patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease (12). Although we were unable to check macrolide susceptibility, it might have been better to choose a three-times-per-week regimen in this case.

The clinical course of EON is reported to be reversed after one month of discontinuation of ethambutol (13), and the cases that experienced severe visual impairment were mostly due to a delay in the discontinuation of ethambutol. In the present case, ethambutol was discontinued before the occurrence of severe visual impairment. However, visual impairment drastically progressed within three weeks. EON should

be carefully checked for during the administration of ethambutol, of course, but it should also be noted that EON can drastically progress even after the withdrawal of ethambutol. A previous literature survey showed that some instances of EON caused a sudden decrease in vision and persistent visual defects, irrespective of the fact that patients were monitored regularly and that treatment was discontinued at the onset of symptoms (14-18). Although severe cases tended to be reported and some cases were treated with a high dose (i.e., >15 mg/kg of ethambutol), to our knowledge, there have been no reported cases with drastically progressing EON even after the withdrawal of low-dose ethambutol. Our case suggests that attention should be paid to the likelihood of EON causing acute vision loss even after the withdrawal of ethambutol.

Because the clinical course in this case was drastic, the

possibility of comorbidity of other mitochondrial optic neuropathies, such as Leber hereditary optic neuropathy (LHON), should be discussed. LHON generally occurs in young patients and in only one eye at first, has various ophthalmologic abnormalities typified by redness or swelling of the optic disc, and has a familial history—none of which were applicable to this case (19). Although the present patient could not be checked for any mitochondrial DNA mutations, we diagnosed him with EON considering the clinical course of the disease.

Apart from the discontinuation of ethambutol, the precautionary and therapeutic measures for EON have not yet been officially defined. A small case series reported that patients achieved visual recovery after the administration of cobalamin (20). EON may be due in part to a deficiency in zinc and copper; however, a routine examination of the levels in patients taking ethambutol has not been recommended (6). In the present case, mecobalamin was initiated; however, the visual acuity had not improved by four months after the discontinuation of ethambutol. EON is unpredictable (5); however, its occurrence should always be considered, and ethambutol should be discontinued as soon as possible when EON is suspected.

In conclusion, EON can occur even in cases of low-dose and short-term ethambutol administration and deteriorate such that irreversible vision loss occurs, even after the withdrawal of ethambutol. A literature review suggested that EON is not a frequent adverse effect, and conventional precaution by careful ophthalmologic monitoring may not contribute to its prevention in some cases; nonetheless, ophthalmologic monitoring should be continued, and we have to inform patients about the possible occurrence of EON in association with the early discontinuation of ethambutol. Further investigations to clarify the specific mechanisms involved and the risk factor of EON are warranted.

The authors state that they have no Conflict of Interest (COI).

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