REVIEW ARTICLE

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Reversible ethambutol-induced optic neuropathy: report of a rare case

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ABSTRACT

BACKGROUND

Ethambutol (EMB) is one of the first-line anti-tuberculosis therapy. One of its precarious side effects is ethambutol-induced optic neuropathy (EON). The ocular manifestations of EON include painless loss of central vision and cecocentral scotomas in the visual field.

CASEDESCRIPTION

A 60-year old man presented with gradual and painless visual loss since 3 months prior to visit. The accompanying symptoms were frequent headache without double vision and photophobia. He had been diagnosed with pulmonary tuberculosis (TB) for 9 months and consumed EMB for 7 months before being advised to discontinue. There was neither history of systemic diseases nor family history of neuropathy. Examination showed reduced visual acuity with positive relative afferent pupillary defect (RAPD) on right eye. Humphrey test showed bilateral generalized visual loss. Ocular computed tomography (OCT) showed retinal nerve fiber layer (RNFL) thickness was within normal limit. Magnetic resonance Imaging (MRI) brain indicated unremarkable result for optic neuropathy. Based on the examinations listed above, this patient was diagnosed as EON and EMB was stopped immediately. Patient was given oral citicoline 1000mg and zinc supplementation for one month. After 1 st and 3 rd month follow up, patient's visual function was gradually improved. The ophthalmic examinations indicated recovery of the visual function.

CONCLUSIONS

This case suggested that an early detection and intervention in patient with EON has promising result in visual outcome. EON is a reversible optic neuropathy if the ocular toxicity is monitored closely among the tuberculosis patients who are prescribed EMB regiment.

Keywords: Ethambutol, optic neuropathy, toxic optic neuropathy

Abbreviations: BCVA = best-corrected visual acuity, EON = ethambutol-induced optic neuropathy, ERG = electroretinogram, IOP = intraocular pressure, mfERG = multifocal electroretinogram, OCT = optical coherence tomography, OU = oculus uterque, RAPD = relative afferent pupillary defect, RNFL = retinal nerve fiber layer, VEP = visual evoked potential.

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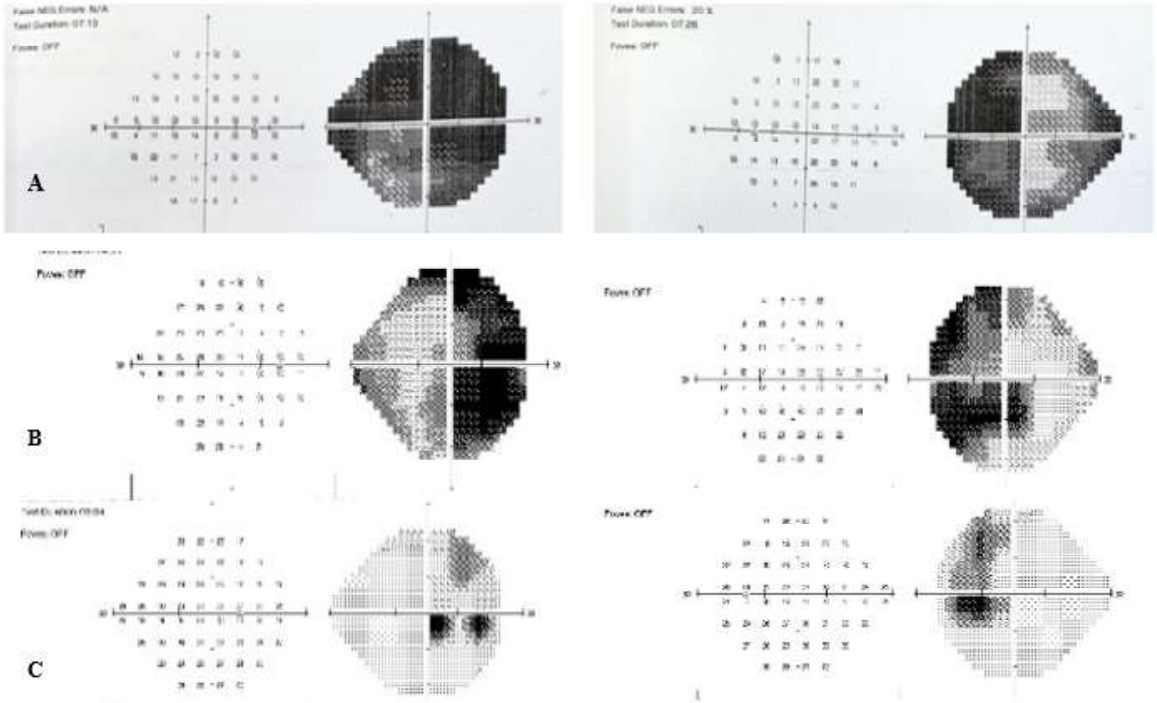
INTRODUCTION

Tuberculosis (TB) is an infectious disease that is found in every country in the world.[1] Indonesia accounts for 44% of global TB cases.[2] One of the first-line medications of TB is ethambutol (EMB), which however has been associated with several side effects.[3,4] The most well-documented and precarious ocular side effect is ethambutol-induced optic neuropathy (EON). The worldwide prevalence of EON in 2013 was 100,000.[3] A study in Taiwan reported that the incidence of EON was 1.29% in 4803 patients with TB and incidence in male patients was higher than in females.[5] According to a retrospective study in Indonesia, EON was recorded in 51 patients with initial presentation of poor visual acuity and mean duration of EMB therapy of 6.2 months.[6] The diagnosis of EON is commonly established after the presence of visual symptoms. The typical clinical manifestations of EON are painless, subacute, and bilateral loss of vision. These manifestations may begin between 1 – 36 months after receiving EMB, but in general EON may develop at 9 months of treatment.[3] Several assessments such as visual acuity and visual fields examination, visual evoked potential (VEP), multifocal electroretinogram (MfERG) and retinal nerve fiber layer (RNFL) thickness are commonly used to detect early and subclinical toxicity.[3,7] At the beginning, the optic nerve appears normal, but as the disease progresses, optic atrophy might present, which indicates irreversible damage. Several risk factors such as hypertension, renal disease and age of more than 65 years are related to a greater risk of EON, although EON is believed to be dose- and duration-dependent.[3,7] The toxicity of ethambutol has been reported to be reversible following early detection of EON. If the patient initially presents with optic disc pallor, the prognosis of EON is considered poor. Early detection and immediate EMB discontinuation are pivotal in impeding irreversible damage. Besides ethambutol cessation, several studies mentioned that citicoline and zinc administration in EON patients produces gives a better outcome. However, there has been no established therapy yet to restore ganglion cell loss due to EON. Thus, it is necessary to detect EON as soon as possible to prevent severe outcome.[5,7] In the present case report, we aimed to report an EON case that came to our hospital recently, to evaluate the clinical characteristics of EON, and to show that early detection of EON can prevent further damage.

CASE REPORT

A 60-year-old man came with bilateral gradual and painless visual loss since 3 months prior to visit. The accompanying symptoms were frequent headache without photophobia and double vision. There was neither history of metabolic diseases nor family history of neuropathy. The patient had been diagnosed with pulmonary TB for 9 months and consumed anti-tuberculosis drugs ever since. The patient took an anti-tuberculosis fixed-drug combination which contains EMB 15mg/kg/day. Previously, he had seen an ophthalmologist regarding his visual loss complaint, when he was advised to immediately discontinue EMB therapy and was given oral corticosteroids for a week. Then, the patient was referred to our outpatient department ward for further investigation. The vital signs were within normal limits. Initial visual acuity (VA) on the right eye was 2/60 and on the left eye 5/60. Left and right pupillary light reflexes were normal, but positive relative afferent pupillary defect (RAPD) was present on the right eye. There was also increased lens opacity on the left eye, indicating mature cortical cataract. Funduscopic examination showed normal optic discs. Humphrey visual field testing was done to assess patient's visual field (VF), showing bilateral generalized visual loss with visual field index (VFI) of 13% and mean deviation (MD) of -26.59 dB on the right eye, and VFI of 43% and MD of -19.9 dB on the left eye (as shown in Figure 1).



Figures 1. Humphrey visual field testing at initial visit (A), 1st month follow up (B) and 3rd month follow up (C)
A : Humphrey visual field testing at initial visit showed generalized visual loss on both eyes
B : During 1 st month follow up showed improvement; bitemporal hemianposia
C : At 3 rd month follow up showed reversible visual field defect compared to initial visit

Color vision and contrast sensitivity test were not performed due to patient's poor VA. Optical coherence tomography (OCT) examination found that the retinal nerve fiber layer (RNFL) thickness oculus uterque (OU, both eyes) was within normal limit, indicating no significant degeneration of optic (as shown in Figure 2). MRI brain scan showed no significant result for acute optic neuropathy, but in relation to patient's clinical presentation, a subacute phase should be considered. Based on history taking and ocular examinations, this patient was diagnosed as EON. Since the patient had already stopped taking EMB for 2 months prior to visit, we prescribed oral citicoline 1000mg od and zinc supplementation od for 1 month. He was also advised to visit his internist regarding the continuity of his anti-tuberculosis medication. At 1st month follow up, patient's VA was 6/45 for the right eye and 3/60 for the left eye. Both VA and VF were gradually improved at 3rd month follow up. VA became 6/18 and 3/60 for the right and left eye, respectively. Humphrey visual field testing revealed remarkable improvement, VFI 84% and MD -3.98 dB for right eye and VFI 87% and MD -4.20 dB for left eye. Relative afferent pupillary defect on right eye became negative, and no recurring symptoms were present. It is possible that left ocular VA did not significantly improve due to lens opacity, hence we planned cataract extraction as the next step of treatment. Figure 2 and Table 1 explain the improvement in visual fields at each given time. Written informed consent was obtained from the patient for publication of this article and any accompanying images.

DISCUSSION

The onset of ocular symptoms of EON varies from days to months after EMB treatment. The safe dose of EMB has not been established, but it has been reported that EMB therapy at more than 15mg/kg/day may increase the incidence of EON.[8] In previous studies, the population of individuals aged 22–90 years (mean 66.9 years)

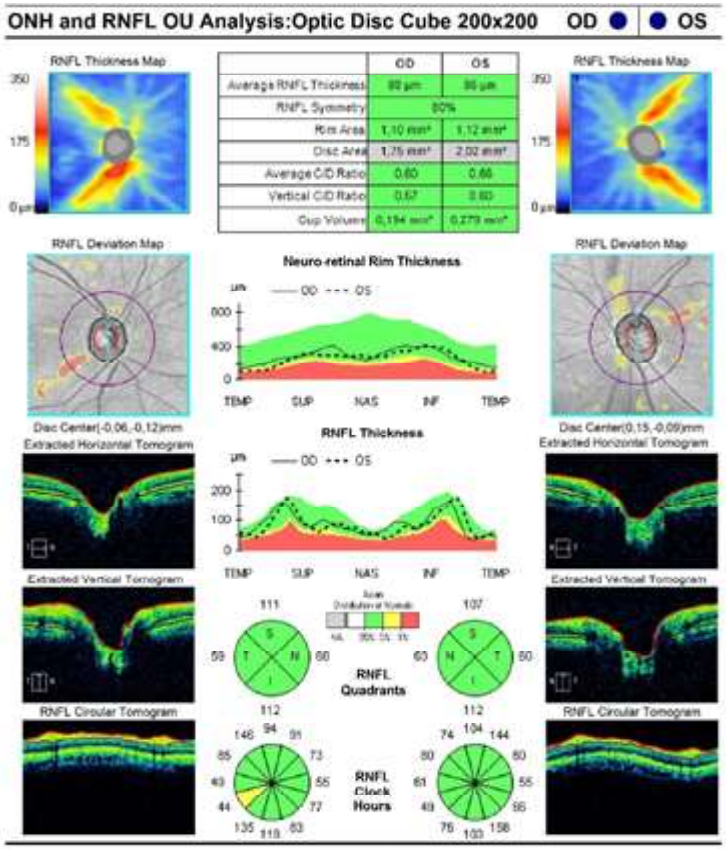


Figure 2. Initial ocular computed tomography (OCT) showed no significant loss of retinal nerve fiber layer (RNFL)

with history of EMB therapy develops EON. The mean EMB dosage was 14.5mg/kg/day and duration of treatment was 1 to 21 months.[1,5] This is similar to our patient's characteristics and history of medication. Our patient was 60 years old and received EMB at 15mg/kg/day. After a 6-month period of medication, the patient had his first visual symptoms which presented as visual loss. Typically, patients with EON complain of subacute, bilateral, painless, and symmetrical central visual loss, which is also in line with our case.[3] Humphrey visual field testing in this case showed bilateral generalized visual loss and in the next 3rd months of follow up, the grey-scale images on Humphrey visual field testing show a cecocentral scotoma, which is similar to previous studies where visual field examination mostly revealed central or cecocentral scotoma.[3] Ocular computed tomography examination in the 1st month of follow-up shows that RNFL thickness was within normal limits. In another longitudinal study performed by Han et al.,[9] the RNFL thickness was within the normal range after the patients stopped taking the drug. In a recent study, Kim and Park [10] reported increase in RNFL thickness among tuberculosis patients receiving ethambutol in the dosage range of 15 to 19 mg/kg/day. It is important to do OCT examination in

Table 1. Humphrey visual field testing during initial assessment and follow ups

		Initial assessment	1st follow up	3rd follow up
VFI	OD	13%	48%	84%
	OS	43%	58%	87%
MD	OD	-26.59 dB	-17.18 dB	-3.98 dB
	OS	-19.9 dB	-13.8 dB	-4.20 dB

VFI: Visual Field Index, MD: Mean deviation

Written informed consent was obtained from the patient for publication of this article and any accompanying images

EON patient to investigate structural changes to particular retinal layers.[11] Our patient showed gradual improvement in both VA and VF after EMB cessation and start of oral citicoline 1000mg od and zinc supplementation therapy. This can be attributed to a previous Taiwanese study which mentioned visual improvement in 50% of the subjects after discontinuation of EMB.[5] Ethambutol acts by inhibiting mycobacterial cell wall synthesis through its metal chelating properties. The similarity between human mitochondria and bacterial cell wall might lead to accumulation of reactive oxygen species in ocular cells, thus resulting in apoptosis and optic nerve degeneration.[8] Previous studies have shown that EMB in canines might synthesize a metabolite which significantly decreases the zinc concentrations in ocular tissue.[12]

Zinc is present in high concentrations in the retina and choroid, therefore zinc deficiency will affect the physiological ocular function, because it plays a role as cofactor in several ocular enzymes.[13] The mechanism of EON is believed to be due to inhibition of lysosomal activity and to zinc chelation.[3] A previous study stated that zinc plays an important role in EON.[14] Inhibition of zinc chelation can reduce its cytotoxicity to the retinal ganglion cells.[14] Another study stated that the number of retinal ganglion cells decreased in rats which were introduced to EMB, hence it is believed that retinal ganglion cell disturbance plays a major role in EON manifestation.[15] Our patient was given zinc supplementation in order to suppress the apoptotic rate of the retinal ganglion cells. Citicoline 1000 mg was also prescribed to the patient. According to a previous study, retinal ganglion cell damage caused by EON can be suppressed by citicoline administration as shown in the finding that the number of retinal ganglion cells in rats with EMB intoxication receiving citicoline was higher than in the other group not receiving citicoline.[6] Systemic diseases such as hypertension, diabetes mellitus and renal failure can affect the visual recovery of EON.[3] Our patient did not have any underlying diseases, and the final visual outcome was remarkably improved. Currently, there is no effective treatment for ganglion cell damage due to EON. Primary prevention is considered the best management. Patients with ethambutol therapy should be informed regarding the adverse effect and the need for periodical ocular screening. Ocular examination (visual acuity, visual field testing, color vision testing and funduscopy) should be performed prior to treatment with ethambutol.[3]

This case report has several limitations. More specific ocular examinations such as mfERG and VEP should have been performed during initial and follow visit. These examinations could have given information about visual function before and after treatment and used as a parameter to evaluate treatment efficacy.

CONCLUSION

It is still debatable whether visual disturbance in EON is reversible. However, immediate ethambutol cessation might improve the visual impairment of the patients. This case report shows that early detection of EON in pulmonary TB patients who are taking ethambutol and complain of visual loss may reverse the visual defect. We can conclude that the reversibility of EON relies on early detection and intervention. Thus, it is necessary for an ophthalmologist to monitor patients with ethambutol therapy during the treatment period.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTION

S.N was the ophthalmologist who diagnosed and was responsible for the management of this patient. All authors contributed equally to the presentation of case report and the manuscript. S.N supervised the case report and final manuscript.

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There are no financial conflicts or interest to disclose.

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