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Ethambutol optic neuropathy with correspondent chiasmitis manifestation in magnetic resonance imaging

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Abstract:

We present a case of an older patient with toxic chiasmatic optic neuropathy accompanied by bitemporal hemianopia associated with ethambutol use. The patient experienced gradual visual defect recovery that was concurrent with an improvement of chiasmal enhancement in the repeat magnetic resonance imaging performed at his 6-month follow-up. However, his visual field pattern sharply changed to left inferior homonymous quadrantanopia because of a new episode of occipital lobe infarction. After 2 years, the patient's visual function reached the best-corrected visual acuity of 20/20 in both eyes, although he had the sequela of homonymous quadrantanopia related to the infarction. Optical coherence tomography revealed that the loss on the macular ganglion cell–inner plexiform layer was related to retrograde transsynaptic degeneration caused by ethambutol-related chiasmopathy.

Keywords:

Bitemporal hemianopia, ethambutol, macular ganglion cell–inner plexiform layer, optic chiasm, toxic optic neuropathy

Introduction

The incidence of ethambutol optic neuropathy (EON) in patients with tuberculosis receiving ethambutol treatment was reported to be at least 1.29%. The vision recovery rate after discontinuation of ethambutol was 50% at 6-month follow-up, according to a retrospective 10-year study in southern Taiwan.^[1] Older age, hypertension, and renal diseases are major risk factors for EON.^[2] Central or cecocentral scotoma is a common visual field (VF) defect pattern observed in EON, whereas bitemporal hemianopia with vertical margination and superimposed central or cecocentral scotoma are relatively rare.^[3] Damage from ethambutol use may involve several regions of the neuroretina; damage involving deeper

retinal layers is diagnosed using multifocal electroretinographic findings, damage affecting papillomacular retinal nerve fibers is documented by optical coherence tomography (OCT), and damage caused to crossing fibers within the chiasm is indicated by bitemporal VF loss. A case of EON due to ethambutol overdose exhibiting predominant chiasmal involvement indicated that the severity of neuropathy may correlate with magnetic resonance imaging (MRI) findings.^[4] A related case report described concurrent improvement of retinal nerve fiber layer (RNFL) thickness and VF function, highlighting a potentially reversible characteristic of EON in both function and structure.^[5] Our case involved optochiasmatic neuropathy with bitemporal hemianopia even when exposed to a normal therapeutic dose of ethambutol. The patient's visual function could be recovered,

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although the macular ganglion cell–inner plexiform layer (mGC-IPL) loss remained, which may indicate a potential diagnostic and predictive value of OCT for toxic optic neuropathy.

Case Report

A 73-year-old man visited our ophthalmic clinic reporting acute-onset bilateral painless blurred vision. Initially, his best-corrected visual acuity (BCVA) was 20/400 in the right eye (OD) and 20/400 in the left eye (OS), with an Ishihara color test result of 13/15 in each eye. He denied having undergone eye surgery, and he had no trauma history. He reported having hypertension, Type 2 diabetes mellitus, and hyperuricemia. He had been receiving ethambutol, isoniazid, and rifampin for tuberculosis treatment for 5 months. He exhibited normal eye position and had free extraocular muscle movement without a relative afferent pupillary defect. The patient's slit-lamp examination revealed a normal anterior segment except for severe nuclear sclerosis in both eyes (OU). His dilated fundus examination revealed a normal macula and pinkish disc with a cup-to-disc ratio of 0.3 in both eyes. Automated perimetry (Humphrey SITA-Fast 24-2; Carl Zeiss Meditec Inc., Dublin, CA, USA) revealed bitemporal hemianopia with a mean deviation of -11.42 dB OD and -15.88 dB OS [Figure 1a]. The initial OCT (Carl Zeiss Meditec Inc.) revealed no mGC-IPL loss in both eyes [Figure 2a]. Fundus angiography indicated unremarkable findings. Under the suspicion of a lesion at the chiasm, brain MRI was arranged. This study revealed predominant enhancement at the optic chiasm in the coronal T1-weighted sequence [Figure 3a]. On the basis of his medical history, he was advised to discontinue ethambutol immediately. Laboratory testing indicated normal complete blood count results with normal vitamin B₁₂ and zinc levels.

After 2 months, his BCVA remained at 20/400 OU and he had an Ishihara test result of 1/15 (OU), although he had discontinued oral ethambutol. Due to persistent severe blurry vision, he underwent bilateral unremarkable phacoemulsification and intraocular lens implant surgery. After discontinuation of ethambutol for 5 months, his BCVA improved slightly to 20/100 OD and 20/60 OS, and MRI revealed nearly normal signal intensity in the area of chiasma [Figure 3b]. After 5.5 months, his VF pattern revealed improvement in scotoma with a mean deviation of -2.14 dB OD and -3.79 dB OS [Figure 1b] and visual acuity of 20/30 OD and 20/50 OS. At his 6-month follow-up, his BCVA had improved to 20/20 OU. Due to his clinical recovery course, bilateral optic neuritis secondary to neuromyelitis optica or infiltrative optic neuropathy would have been ruled out.

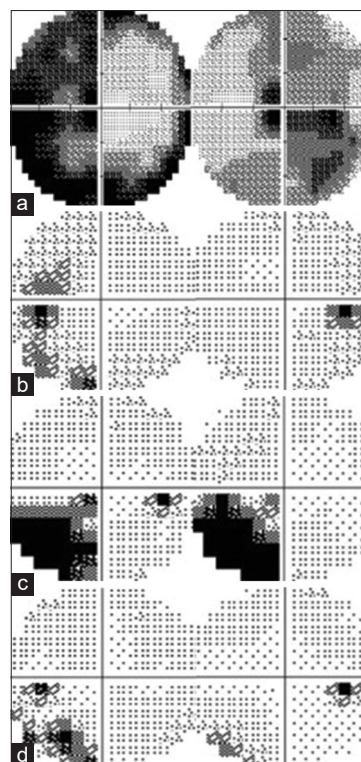


Figure 1: Automated visual field. (a) Bitemporal hemianopia is present in the 5th month after starting ethambutol, with a mean deviation of -11.42 dB in the right eye (OD) and -15.88 dB in the left eye (OS). (b) Improvement in the patient's visual field was observed after discontinuation of ethambutol for 6 months, with a mean deviation of -2.14 dB OD and -3.79 dB OS. (c) Bilateral homonymous left inferior quadrantanopia was noted (mean deviation, -6.30 dB OD and -5.37 dB OS). (d) Considerable visual field pattern improvement (mean deviation, 1.14 dB OD and -2.22 dB OS) was noted at the 6-month follow-up

However, the patient had a newly developed lower scotoma in his left eye several months later. At that time, his VF pattern exhibited left inferior homonymous quadrantanopia with a mean deviation of -6.30 dB OD and -5.37 dB OS [Figure 1c]. MRI revealed hyperintensity in the right occipital region on both T1- and T2-weighted images [Figure 3c and d], indicating a subacute infarction. Even after experiencing a stroke, his BCVA remained at 20/20 OU, and his VF pattern exhibited minimal homonymous quadrantanopia with a mean deviation of -1.14 dB OD and -2.22 dB OS [Figure 1d] after 6 months. In the patient's last OCT, notable retrograde thinning of the mGC-IPL at the nasal side of the macula (OU) was observed, which probably resulted from the previous toxic chiasmopathy [Figure 2b].

Discussion

This case report describes EON that involved the chiasma with a bilateral hemianopia VF defect. The patient exhibited a reduction of mGC-IPL thickness in the nasal sector of the macula in both eyes during the longer follow-up period. The retrograde transsynaptic degeneration loss of the mGC-IPL was related to toxicity

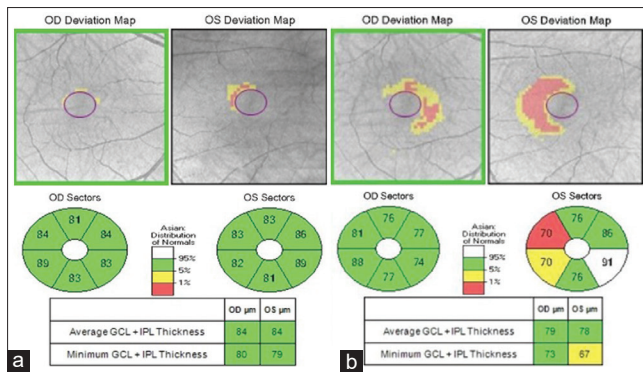


Figure 2: Optical coherence tomography with deviation map of macular ganglion cell–inner plexiform layer thickness. (a) The initial optical coherence tomography revealed normal average macular ganglion cell–inner plexiform layer thickness. (b) In the final optical coherence tomography, the minimum macular ganglion cell–inner plexiform layer thickness was 73 μm (right eye [OD]) and 67 μm (left eye [OS]), and the average macular ganglion cell–inner plexiform layer thickness was lower in both eyes compared with the initial optical coherence tomography. The nasal part of the macular ganglion cell–inner plexiform layer appeared to have more obvious atrophy than the temporal part. mGC-IPL = macular ganglion cell–inner plexiform layer.

rather than to the later stroke episode; we posited that stroke-related transsynaptic degeneration loss was less likely to occur within 1 year.^[6]

The pathogenesis of EON has not been well established. Ethambutol reportedly impairs autophagic flux by inhibiting the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin signaling pathway and causes apoptotic death in the neuronal cells of the retina.^[7] The metal-chelating effect of ethambutol presumably disrupts oxidative phosphorylation and consequently mitochondrial function.^[8,9] Intracellular zinc is known to play a major role in the accumulation of ethambutol in autophagosomes and vacuolated lysosomes, and marked Zn^{2+} accumulation leads to insufficient autophagy.^[10,11] By contrast, Yoon *et al.*^[12] proposed that ethambutol causes loss of retinal ganglion cells (RGCs) through the mechanism that depletes intracellular zinc, causing neither intracellular zinc accumulation nor glutamate excitotoxicity.

In a Taiwanese study, recovery rates of 50% were reported among EON cases, with the recovered patients commonly exhibiting improvement in their VF function more than 6 months after cessation of ethambutol treatment, with an average improvement of two lines on the Snellen chart.^[1] A case series reported a 20% full recovery rate in patients aged >60 years compared with 80% in the younger group, indicating that younger people have a higher recovery rate.^[13] Another paper concluded that the resolution of EON typically occurs within 3 months after the cessation of ethambutol.^[14] Our patient had comorbid diabetes mellitus and smoking history as well as MRI-confirmed chiasmopathic damage; these factors may account for his longer recovery time.

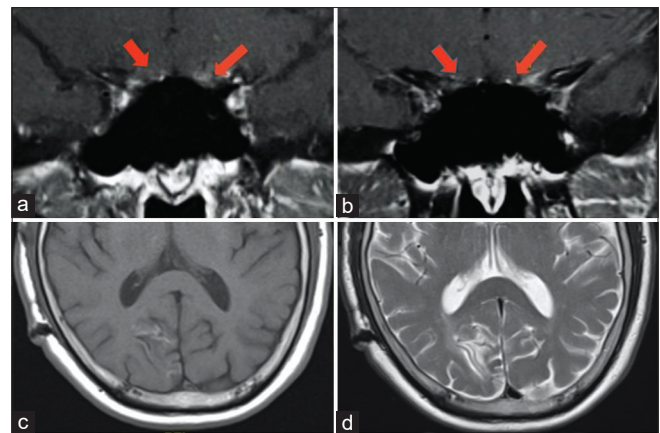


Figure 3: Brain magnetic resonance imaging. (a) Coronal T1-weighted image showing a hyperintense signal in the chiasm with left side predominant enhancement (Arrow). (b) Normalization of the signal in the chiasm after discontinuation of ethambutol for 5 months (Arrow). (c and d) Magnetic resonance imaging revealing a hyperintense signal in the right occipital region in T1- and T2-weighted images

Chiasmopathy is thought to occur because of proximal progression of optic neuropathy, which may suggest a genetic role in the pathogenesis of chiasmopathy.^[15]

In an animal experiment, Kinoshita *et al.*^[16] found that a photopic negative response was significantly attenuated, which indicated damaged function in the RGCs of cynomolgus monkeys. In patients with EON, a decrease of 20%–79% in the RNFL in OCT represents a wide RNFL loss with high variation.^[17,18] An early thickness reduction was found in the mGC-IPL, which may precede the decrease in peripapillary RNFL as well.^[19,20] Regarding the diagnostic value of toxic optic neuropathy, nasal mGC-IPL appeared to be superior to temporal mGC-IPL, indicating the impact of the papillomacular bundle.^[14] Lee *et al.*^[21] reported a negative correlation between mGC-IPL thickness in the nasal sector and visual potential. One study demonstrated that the average minimum value for the mGC-IPL was 64.0 μm in a suspected case of EON.^[14] However, we believe that a decrease in the thickness of the mGC-IPL may serve as a sensitive but nonspecific diagnostic marker in EON.

In conclusion, our patient exhibited a rare case of bitemporal hemianopia resulting from ethambutol toxicity; corresponding chiasmatic enhancement was observed on MRI, along with a reduction in thickness of the nasal part of the mGC-IPL. Longer visual recovery time may be required in older patients with concurrent underlying diseases and deeper optic chiasm involvement.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands

that his names and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed. Informed consent was obtained from the patient according to the Declaration of Helsinki, 1964 version.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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