

Utility Of Optical Coherence Tomography In The Evaluation Of Patients With Ethambutol-Induced Optic Neuropathy

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Abstract

In this study, optical coherence tomography (OCT) was used to evaluate retinal thickness in two patients with optic neuropathy who had recently discontinued ethambutol. OCT was used to measure retinal nerve fiber layer (RNFL) thickness and to map the RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL). Decreased RNFL thickness was observed in one case. However, the combined RNFL, GCL, and IPL map showed significant decreases in retinal thickness in both cases, suggesting that ethambutol likely affects the GCL as well as the RNFL. I propose that the GCL thickness should be considered in addition to the RNFL thickness while monitoring ethambutol-induced optic neuropathy.

INTRODUCTION

Optic neuropathy is the most important potential side effect of ethambutol. The reported incidence of this toxicity varies widely in different studies, ranging from 0.5% to more than 35%.^{1, 2} Although the optic nerve toxicity of ethambutol is well known, this agent may also be toxic to the retina.³ Animal studies have demonstrated ethambutol toxicity in retinal ganglion cells.^{4, 5}

Optical coherence tomography (OCT), which is a well-recognized technique used to image the cross-sectional microstructure of the retina, has also been used to measure retinal thickness.

Although several reports have investigated the retinal nerve fiber layer (RNFL) thickness by using OCT, 6-12 to my knowledge, no studies have focused on retinal ganglion cell layer (GCL) thickness in the evaluation of ethambutol-induced optic neuropathy. Herein, the value of OCT is reported in two patients with ethambutol-induced optic neuropathy.

CASE PRESENTATION

Case 1

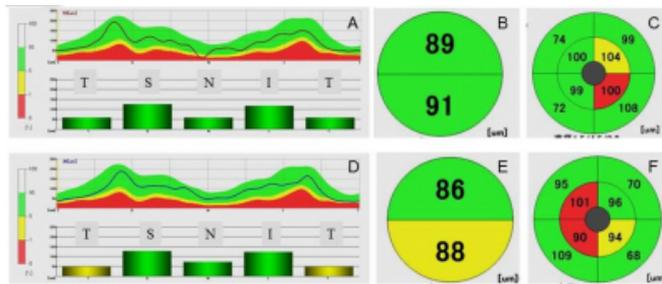
A 77-year-old man, who was being treated for nontuberculous mycobacteriosis, initially presented with a 3-month history of gradual, painless loss of vision in both eyes. He had received ethambutol treatment for 8 months at the standard dosage. His visual complaints had continued to

worsen up to presentation. On ophthalmic examination, the best-corrected visual acuity (BCVA) was 0.3 in the right eye and 0.4 in the left eye. On slit-lamp examination, mild cortical opacities were detected in both lenses. The ocular pressures were normal and the fundus examination showed no optic disc pallor in either eye. Optical coherence tomography (OCT; RS-3000, NIDEK, Japan) was used to measure retinal nerve fiber layer (RNFL) thickness in a circular area centered on the optic disc. RNFL thickness measurements were averaged for each quadrant of this circle and for the circular area overall. Further, OCT was used to map the RNFL, ganglion cell layer (GCL), and inner plexiform layer (IPL). The latter two maps were overlapped in order to measure retinal thickness at the macula. Measurements were obtained at an inner ring (1.5–4.5 mm from the central fovea) and at an outer ring (4.5–9.0 mm from the central fovea). No measurement was obtained at the central fovea. In the right eye, the mean RNFL thicknesses at the temporal, superior, nasal, and inferior quadrants were 57 μm , 125 μm , 57 μm , and 117 μm , respectively; in the left eye, these values were 48 μm , 127 μm , 72 μm , and 123 μm , respectively (Figure 1A and D). The combined RNFL, GCL, and IPL map showed that the respective thicknesses at the superior and inferior segments were 89 μm and 91 μm in the right eye; in the left eye, these values were 86 μm and 88 μm , respectively (Figure 1B and E). In addition, the combined RNFL, GCL, and IPL map revealed that the thicknesses at the superotemporal, inferotemporal, superonasal, and inferonasal quadrants were 100 μm , 99 μm ,

104 μm, and 100 μm, respectively, at the inner ring in the right eye; in the left eye, these values were 96 μm, 94 μm, 101 μm, and 90 μm, respectively (Figure 1C and F). The measurements at the outer ring were 74 μm, 72 μm, 99 μm, and 108 μm, respectively, in the right eye; in the left eye, the respective values were 70 μm, 68 μm, 95 μm, and 109 μm (Figure 1C, and F).

Figure 1

Case 1: Results of optical coherence tomography examination (A‐C: right eye, D‐F: left eye) A and D: RNFL map, B and E: RNFL + GCL + IPL map (9.0 mm), C and F: RNFL + GCL + IPL map (1.5/4.5/9.0 mm). Abbreviations: RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; T, temporal; S, superior; N, nasal; I, inferior



The results showed significant decreases in the RNFL thickness at the temporal quadrant and in the retinal thickness at the inferior quadrant in the left eye. The decrease was much more marked in the combined RNFL, GCL, and IPL map compared to in the RNFL map. A comparison with the normative database showed that the combined thickness of the RNFL, GCL, and IPL as measured at the inner ring was decreased in comparison to > 99% of the population in both eyes. Although the BCVA gradually improved to 1.2 in both eyes over a period of 6 months, the OCT findings remained stable.

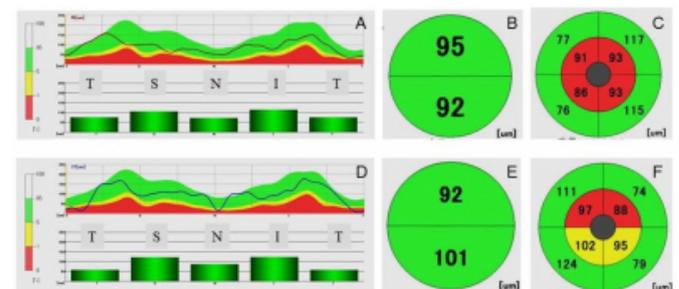
Case 2

A 70-year-old woman, who was being treated for nontuberculous mycobacteriosis, initially presented with a 3-month history of gradual, painless loss of vision in both eyes. She had received ethambutol treatment for 12 months at the standard dosage. Her visual complaints had continued to worsen up to presentation. On ophthalmic examination, the BCVAs in the right and left eyes were 0.09 and 0.15, respectively. On slit-lamp examination, mild cortical opacities were detected in both lenses. The ocular pressures were normal and the fundus examination showed no optic disc pallor in either eye. On OCT examination, the mean

RNFL thicknesses at the temporal, superior, nasal, and inferior quadrants were 75 μm, 105 μm, 71 μm, and 113 μm, respectively, in the right eye; in the left eye, these values were 57 μm, 121 μm, 86 μm, and 123 μm, respectively (Figure 2A and D). The combined RNFL, GCL, and IPL map showed that the respective thicknesses at the superior and inferior segments were 95 μm and 92 μm, in the right eye; in the left eye, these values were 92 μm and 101 μm, respectively (Figure 2B and E). The combined RNFL, GCL, and IPL map revealed that the thicknesses at the superotemporal, inferotemporal, superonasal, and inferonasal quadrants were 91 μm, 86 μm, 93 μm, and 93 μm, respectively, at the inner ring in the right eye; in the left eye, these values were 88 μm, 95 μm, 97 μm, and 102 μm, respectively (Figure 2C and F). The respective measurements at the outer ring were 77 μm, 76 μm, 117 μm, and 115 μm in the right eye and 74 μm, 79 μm, 111 μm, and 124 μm in the left eye (Figure 2C and F).

Figure 2

Case 2: Results of optical coherence tomography examination (A‐C: right eye, D‐F: left eye) A and D: RNFL map, B and E: RNFL + GCL + IPL map (9.0 mm), C and F: RNFL + GCL + IPL map (1.5/4.5/9.0 mm). Abbreviations: RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; T, temporal; S, superior; N, nasal; I, inferior



The results showed no significant decrease of the RNFL thickness at any of the quadrants. However, the combined RNFL, GCL, and IPL map as measured at the inner ring showed significant decrease of the retinal thickness. Although the BCVA gradually improved to 0.3 in both eyes over a period of 6 months, the OCT findings remained stable.

DISCUSSION

Although the prognosis of visual recovery from ethambutol-induced optic neuropathy is highly

variable, toxicity from ethambutol is traditionally described as reversible when the drug is discontinued, and vision is

believed to recover gradually over weeks to months. 1 However, permanent visual impairment has been described even with timely cessation of ethambutol.

Recent studies on RNFL thickness examined by OCT in cases of ethambutol-induced optic neuropathy have described significant RNFL thickness diminution. 6-9 In contrast, Kim et al. 11 found that the RNFL thickness was not significantly different between patients with ethambutol-induced optic neuropathy in the early stage and normal controls. Furthermore, Goto and Mimura 12 reported that the RNFL thickness showed an increase in the early stage. Zoumalan et al. 10 reported reversible RNFL changes to retinal ganglion cell axonal swelling, with gradual resolution after cessation of ethambutol. Although several of these reports investigated the RNFL thickness, 6-12 to my knowledge, no studies have focused on the GCL thickness. In this series, case 1 showed complete recovery of BCVA, whereas case 2 did not completely improve. I speculate that this discrepancy is due to differences in GCL thickness; i.e., the GCL thickness was reduced in case 2 compared to case 1. Further studies with additional cases will need to be evaluated in order to prove this speculation.

The mechanism of ethambutol toxicity remains unknown, but several hypotheses have been proposed. The pathogenesis of ethambutol-induced optic neuropathy is thought to be related to the accumulation of zinc in lysosomes, leading to lysosomal membrane permeabilization and subsequent alteration of mitochondrial function and apoptosis of retinal ganglion cells. 3, 8, 13 Heng et al. 4 hypothesized that visual loss was caused by a glutamate-related excitotoxicity effect on retinal ganglion cells in rats.

Although the current findings were based on only two cases and OCT examination before ethambutol treatment was not available, the results suggest that ethambutol affects the retinal GCL as well as the RNFL. I propose that retinal GCL

thickness should be considered in addition to RNFL thickness when monitoring ethambutol-induced optic neuropathy.

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