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Early stage ethambutol optic neuropathy: retinal nerve fiber layer and optical coherence tomography

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PURPOSE. *To evaluate retinal nerve fiber layer (RNFL) thickness with optical coherence tomography (OCT) in early stage ethambutol optic neuropathy.*
METHODS. *The RNFL thickness of 20 eyes of 10 patients who developed optic neuropathy after taking ethambutol and visited within 6 months after onset were analyzed and compared with those of 54 eyes of 29 healthy age-matched controls. The mean age was 67.40±10.25 years for the patients with toxic optic neuropathy and 66.78±10.60 for the control group (p=0.948). A full ophthalmologic examination including RNFL evaluation with fast RNFL thickness (3.4) scanning using a Stratus OCT (Carl Zeiss Meditec, Dublin, CA) was performed.*
RESULTS. *RNFL thicknesses associated with early ethambutol optic neuropathy were as follows: temporal 75.35±15.77 µm, superior 124.05±24.62 µm, nasal 75.15±24.23 µm, inferior 127.60±22.91 µm, and the average was 100.83±16.56 µm. There was no significant difference between the RNFL thickness of the patients with the early stage of ethambutol optic neuropathy and those of the control group. The thickness of RNFL was greater in the temporal quadrant than the nasal quadrant, although not statistically significant.*
CONCLUSIONS. *RNFL thickness associated with ethambutol optic neuropathy during the early stages was not different from the controls. Although not statistically significant, the relative thickening of temporal RNFL in our patients might represent a mild swelling of the papillomacular bundle. (Eur J Ophthalmol 2009; 19: 466-9)*

KEY WORDS. *Ethambutol, Optical coherence tomography, Retinal nerve fiber layer thickness, Toxic optic neuropathy*

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INTRODUCTION

Ethambutol [(d)-2.2'-(ethylene-diimino) di-1-butanol] is an oral chemotherapeutic agent specifically effective against Mycobacterium (1). The most common toxic effect of ethambutol is optic neuropathy. The incidence of ethambutol induced optic neuropathy has been reported to be 1% in the therapeutic dose range (15–25 mg/kg/day) (2).

The symptoms of ethambutol optic neuropathy are dyschromatopsia, decreased visual acuity, and visual field defects; all are based on the subjective report of the patient. There are no abnormal findings in the fundus observed at the early stage of optic neuropathy within 6 months of the onset of visual deterioration (3). The purpose of this study was to evaluate the efficacy of evaluation of retinal nerve fiber layer (RNFL) thickness with optical coherence tomography (OCT), for an evaluation of early stage abnormalities associated with a relatively rare population with ethambutol optic neuropathy.

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METHODS

The RNFL thickness of 20 eyes from 10 patients (4 male and 6 female) who developed optic neuropathy after taking ethambutol and visited our clinic within 6 months after the onset of symptoms (mean interval 2.03 months, from 2 weeks to 4 months) was analyzed and compared with those of 54 eyes from 29 healthy age-matched controls (14 male and 15 female). The mean age was 67.40±10.25 years in the toxic optic neuropathy group and 66.78±10.60 years in the control group (p=0.948). The doses of medication are shown in Table I. Leber hereditary optic neuropathy (LHON) was ruled out after mutation analysis involving mtDNA mutations at nucleotides 11778, 14484, 3460, and 4171 of LHON. Inclusion criteria were as follows: slowly progressive visual loss accompanied by dyschromatopsia after taking ethambutol, duration of ethambutol of more than 2 months, normal appearance of the optic disc, and absence of symptoms associated with optic neuritis such as pain on ocular movement.

Complete ophthalmologic examinations including the measurement of the best-corrected visual acuity, Ishihara color test with the 14 plates, the Hardy-Rand-Rittler test, the pupillary light reflex test, a slit lamp examination, fundus examination, and a visual field test were performed. The RNFL thickness was evaluated by fast RNFL thickness (3.4) scanning using the Stratus OCT (Carl Zeiss Meditec, Dublin, CA). RNFL thickness was measured at 3.4 mm around the optic nerve. Four quadrants (temporal, superior, nasal, and inferior) and the average thickness were compared in the toxic optic neuropathy and control groups. For statistical analysis, the Mann-Whitney test was used with SPSS version 15.0 and $p<0.05$ was considered statistically significant. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

RESULTS

The mean duration of ethambutol treatment until visual deterioration, and discontinuation of treatment, was 7.15±3.64 months and 0.80±0.89 months, respectively. Nine patients had pulmonary tuberculosis and one patient had tuberculosis meningitis. The interval from visual loss to RNFL thickness evaluation was 2.03 months (range from 2 weeks to 4 months). The mean best-corrected visual acuity was 1.25±0.74 logMAR in the toxic optic neuropathy group and 0.12±0.17 logMAR in the control group (Student *t* test, $p<0.0001$). Twelve of 20 eyes with ethambutol optic neuropathy showed total dyschromatopsia. Three patients showed subnormal (five to nine plate) and one patient figured out 13 of 14 plates. The visual field defects included cecocentral visual field defects in 12 eyes, superior hemifield defects in 2 eyes, left-sided hemianopia in 2 eyes, and no specific abnormal findings in 4 eyes.

TABLE I - CLINICAL CHARACTERISTICS AND DOSAGE OF DRUGS IN PATIENTS WITH TOXIC OPTIC NEUROPATHY

No.	Sex/age, yr	Visual acuity R/L logMar)	Color test* (R/L)	Visual field test	Duration† (mo)	Interval‡ (mo)	Ethambutol (mg/kg/day)
1	F/50	1.4/1.4	5/5.5	CC/CC	10	4	6
2	F/49	0.5/0.7	13.5/13	NL/NL	6	3	12
3	M/72	1.2/1.8	0/0	Sup/Sup	5	1	12
4	M/67	1.8/1.4	0/0	L HA/L HA	6	0.5	18
5	F/80	0.8/0.7	1/ 1	CC/CC	9	2	12
6	F/63	0.5/0.5	1.5/0	CC/CC	3.5	0.25	12
7	F/72	1.4/1.4	5/5.5	CC/CC	6	4	NA
8	M/71	0.7/1.1	0/0	CC/CC	20§	1	12
9	F/77	3.0/3.0	0/0	CC/CC	5	3	NA
10	M/73	0.5/0.8	9.5/8	CC/CC	6	3	12

*Ishihara test, 14 plates.
†Duration of antituberculosis medication.
‡Interval between visual deterioration and first visit to our clinic.
§Recurrent tuberculosis patient.
CC = cecocentral; NL = normal; Sup = superior hemifield defect; HA = hemianopsia; NA = data not available.

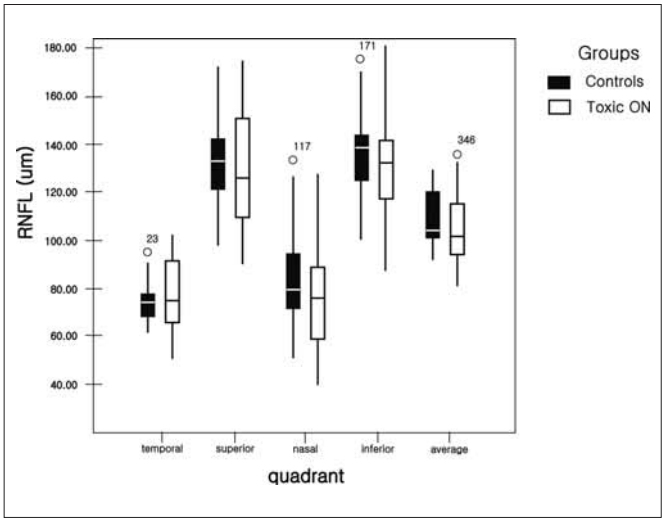

Fig. 1 - *A comparison of retinal nerve fiber thickness between ethambutol optic neuropathy and the control group.*

RNFL thickness during the early stage of ethambutol optic neuropathy and in the controls is shown in Table II. There was no significant difference in the RNFL thickness between the two groups (Fig. 1). However, compared to the controls, in which the temporal RNFL thickness was thinner than nasal RNFL thickness, the temporal RNFL thickness was not different from nasal RNFL thickness (Student paired *t* test, p=0.952) in the ethambutol optic neuropathy group.

DISCUSSION

According to the results of our study, there was no significant difference between the RNFL thickness of the ethambutol optic neuropathy group and the control group measured by OCT. In our study, OCT shows slight decreases in RNFL in three quadrants but a slight increase on the temporal quadrant. Similarly, unaffected carriers of LHON are also known to develop RNFL thickening in the temporal quadrant (4). Moreover, in mice models mimicking LHON, axonal swelling and optic nerve head pseudoedema were observed during the early stage of optic nerve degeneration (5). Therefore, although not statistically significant, the relative thickening of temporal RNFL in our patients might represent a mild swelling of the papillomacular bundle.

In the late stage of ethambutol optic neuropathy, papillomacular bundle was injured primarily (6). This finding can be explained by the effect of ethambutol that raises glutamate levels in the cell thereby decreasing calcium levels in the cytoplasm and increasing mitochondrial calcium; such imbalance in electrolytes results in the disruption of mitochondrial membrane potential (7). Small P-cell axons of the papillomacular bundle have the smallest volume to surface area ratio leaving the least margin of error in a specific setting such as energy depletion. Thus, smallest-caliber axons may have the greatest disadvantage requiring energy dependence in maintaining efficient axoplasmic transport (8).

Zoumalan et al (6) first investigated about the thickness of RNFL in patients with ethambutol optic neuropathy. Diminution of RNFL thickness had been reported to be the most prominent at the temporal quadrant in patients with ethambutol optic neuropathy (9). However, their study had some limitations, such as lack of data on RNFL during the early stage, absence of a detailed description of RNFL thickness in all quadrants, the fact that initial and later RNFL thickness of each patient

TABLE II - RETINAL NERVE FIBER LAYER THICKNESS IN PATIENTS WITH TOXIC OPTIC NEUROPATHY ASSOCIATED WITH ANTI-TUBERCULOSIS MEDICATION AND THE CONTROL GROUP

Quadrant	Ethambutol groups (n=18, µm)	Control groups (n=56, µm)	p value*
Temporal	75.35±15.77	72.57±7.93	0.280
Superior	124.05±26.62	127.98±14.15	0.465
Nasal	75.15±24.23	80.72±17.86	0.292
Inferior	127.60±22.91	133.02±16.71	0.210
Average	100.83±16.56	103.58±10.40	0.330

*Mann-Whitney test.

were not compared, and a sample care of only three patients in which their timing of examinations differed as well, resulting in variable RNFL thickness results. Therefore, our study is ultimately the first to provide a detailed description of RNFL thickness during the early stage of ethambutol optic neuropathy. Follow-up examinations of longitudinal OCT would be helpful in clarifying the changes in RNFL thickness over time and the correlation of RNFL with fundus findings or visual field defects.

In conclusion, objective measurement of RNFL thickness showed no significant difference between the patients with ethambutol optic neuropathy in the early stage and normal controls.

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