Macular thickness as a predictor of loss of visual sensitivity in ethambutol-induced optic neuropathy

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Graphical Abstract

Abstract

Ethambutol is a common cause of drug-related optic neuropathy. Prediction of the onset of ethambutol-induced optic neuropathy and consequent drug withdrawal may be an effective method to stop visual loss. Previous studies have shown that structural injury to the optic nerve occurred earlier than the damage to visual function. Therefore, we decided to detect structural biomarkers marking visual field loss in early stage ethambutol-induced optic neuropathy. The thickness of peripapillary retinal nerve fiber layer, macular thickness and visual sensitivity loss would be observed in 11 ethambutol-induced optic neuropathy patients (22 eyes) using optical coherence tomography. Twenty-four healthy age- and sex-matched participants (48 eyes) were used as controls. Results demonstrated that the temporal peripapillary retinal nerve fiber layer thickness and average macular thickness were thinner in patients with ethambutol-induced optic neuropathy compared with healthy controls. The average macular thickness was strongly positively correlated with central visual sensitivity loss ($r^2=0.878$, $P=0.000$). These findings suggest that optical coherence tomography can be used to efficiently screen patients. Macular thickness loss could be a potential factor for predicting the onset of ethambutol-induced optic neuropathy.

Key Words: nerve regeneration; ethambutol-induced optic neuropathy; optical coherence tomography; peripapillary retinal nerve fiber layer; ethambutol; macular thickness; visual sensitivity; neural regeneration

Introduction

Worldwide, 9.2 million new cases of tuberculosis occur every year and 55% of them take ethambutol to prevent the occurrence of drug-resistance (Wang et al., 2012, 2013; Geyer et al., 2014). As a consequence, the ethambutol-induced optic neuropathy (EON) becomes the most common drug-related optic neuropathy and accounts for 100,000 new cases each year. As a metal chelator, ethambutol has an antibacterial effect on suppressing arabinosyl transferase, which plays an important role in synthesizing the cell walls. Ethambutol triggers the apoptosis cascade in cells by decreasing the levels of oxidative phosphorylation and reactive oxygen species in mitochondria, leading to the leakage of cytochrome C, which is a key activator of apoptosis (Kozak et al., 1998; Pradhan et al., 2010; Cutan et al., 2013; Wang et al., 2013). The unmyelinated and narrow caliber fibers in the papillo-macular bundle, which have the task of conducting central vision, are more vulnerable to ethambutol injury. Thus, EON is characterized by onset of bilateral central vision loss, dyschromatopsia and central scotomas (Wang et al., 2013). Other mitochondrial optic neuropathies exhibit similar symptoms (Pan et al., 2012; Fonkem et al., 2013). A few cases
of EON presented bitemporal hemianopia involving the optic chiasmal region (Kho et al., 2011; Boulanger-Scemama et al., 2013; Geyer et al., 2014). At present, there are no effective treatments for EON (Lee et al., 2008; Chatziralli et al., 2010), but if the clinicians can detect the associated visual loss and discontinue ethambutol administration in the early stage of EON, the irreversible profound visual loss can be avoided (Kakkada et al., 2005).

Glaucoma studies found that the optic nerve impairment or loss preceded visual loss. Previous studies found that the visual function decayed when the thickness of the peripapillary retinal nerve fiber layer (pRNFL) decreased below 75 µm in patients with glaucoma (Kanamori et al., 2003; Costello et al., 2006). If optic nerve impairment or loss precedes the central visual loss, we could screen for optic nerve loss in EON patients treated with ethambutol. Recently, the advancement of a non-invasive imaging technique, spectral domain optical coherence tomography (SD-OCT) with 1.0–2.0 µm resolution in cross-section, is widely used in ophthalmology to measure the thickness of the retinal nerve fiber layer (RNFL) and the retinal ganglion cell layer (Wojtkowski et al., 2004; García-Martín et al., 2014). A previous study demonstrated that pRNFL thickness in EON patients was thinner compared with healthy controls, with the greatest loss in the temporal pRNFL (Chai et al., 2007). However, due to the interferences of optic disc dysplasia, high myopia and blood vessels in pRNFL, the difference in pRNFL thickness between individuals is great. The individual difference of macular thickness without these interferences is small. The macula is mainly composed of retinal ganglion cell bodies which account for 40% thickness of macula (Papchenko et al., 2012), therefore macular thickness can give some representation of optic nerve injury.

We formed a hypothesis that by detecting pRNFL and macular thicknesses with SD-OCT and evaluating their correlations to visual field sensitivity in patients with EON, a sensitive predictor of EON could be established. This could inform ophthalmologists when to discontinue ethambutol treatment to avoid the subsequent visual loss.

**Subjects and Methods**

**Subjects**

A total of 11 EON patients (22 eyes) were consecutively enrolled in this study. Twenty-four healthy subjects (48 eyes) from staff at the Chinese People Liberation Army General Hospital were recruited as healthy controls (Table 1).

Inclusion criteria: the patients with optic neuropathy from Department of Ophthalmology, Chinese PLA General Hospital were recruited in the present study according to the diagnostic criteria for EON (Lim, 2006; Papchenko et al., 2012). (1) Visual loss symptoms after taking ethambutol; (2) more than one primary and two secondary criteria as follows: the primary criteria: abnormal perception of colors (color anomalopia) without other causes, bilateral central visual loss or eccentric visual loss except for central or scocentral scotomas; the secondary criteria: papillary pale and visual loss.

Exclusion criteria: refractive error greater than ±6.00 diopters, an astigmatism of ±2.00 diopters, intraocular pressure greater than 21 mmHg (1 mmHg=0.133 kPa) complicated with other ocular diseases, intraocular surgery history, other diseases affecting the visual field and the optic nerve or visual pathway.

The study was approved by the Ethics Committee of the Chinese PLA General Hospital and was conducted following the Declaration of Helsinki in its currently applicable version. Patients provided written informed consent.

**SD-OCT**

All patients underwent OCT examinations in 3–5 days after a confirmed diagnosis of EON. OCT examinations were performed with SD-OCT (Cirrus HD OCT, Carl Zeiss Meditec Inc., Dublin, CA, USA) and without pupil dilatation. pRNFL was detected by a 3.4-mm circular scan around the optic disc. The following parameters were measured: average pRNFL thickness value (360° measure), four quadrants of pRNFL thickness (superior, nasal, inferior and temporal quadrants), and 12-hour pRNFL thickness (Figure 1A–C). The pRNFL thickness was divided in the six sectors according to glaucoma studies: (temporal (310°–40°), superotemporal (41°–80°), supersonal (81°–120°), nasal (121°–230°), inferonasal (231°–270°), and inferotemporal (271°–310°), and calculated according to the parameters acquired from 3.4-mm circular scanning (Figure 2).

Macular thickness and volume were examined using the device’s standard Macular Cube model (512 × 128), and the macular measurements were included: (1) cube average macular thickness (CAMT) within the diameter of a 6-mm circle in the macula; (2) cube macular volume, macular volume within the diameter of a 6-mm circle; (3) nine sectors of macular thickness according to 1-, 3-, 6-mm Early Treatment Diabetic Retinopathy Study (ETDRS) map, among them the central subfield macular thickness, was the average macular fovea thickness within the diameter of a 1-mm circle (Figure 1D). The observation indexes include average pRNFL thickness (µm), macular volume, and nine sectors of macular thickness. The 3.4-mm circular scan model and standard Macular Cube model (512 × 128) with automatic analysis provide the parameters directly.

**Visual function testing**

All patients with EON underwent ophthalmological examinations, including best-corrected visual acuity assessment and visual field sensitivity evaluated by a Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc. Dublin, CA, USA) using Goldmann size III stimulus within 3–5 days after a confirmed diagnosis of EON.

The best-corrected visual acuity was assessed by a Snellen Eye Chart (decimal acuity) and converted into logMAR notations (decimal acuity). Finger counting, hand motion, and light perception were converted into logMAR equivalents of 1.85, 2.3, 2.7 and 3.0 (Schulze-Bonsel et al., 2006). For visual sensitivity loss, the severity of visual field sensitivity defects was evaluated according to total deviation measured in decibels. The correlation of the average visual field sensitivity of 12 central points (an area roughly equivalent to the...
Table 1 Demographic and clinical overview of subjects in this study

|                | EON-pRNFL | EON-macular | Healthy controls |
|----------------|-----------|-------------|-------------------|
| Subjects (n)   | 9(17 eyes)| 7(13 eyes)  | 23(46 eyes)       |
| Gender (n)     |           |             |                   |
| Female         | 2         | 3           | 10                |
| Male           | 7         | 4           | 13                |
| Age (year)     |           |             |                   |
| Mean±SD        | 42.8±15.4 | 43.5±19.3   | 43.8±12.7         |
| Min–Max        | 23–72     | 23–72       | 25–72             |
| Disease duration (month) | Mean±SD | 3.12±1.21 | 2.85±1.23 | N/A |
| Eyes (n)       | 17        | 13          | 46                |

There were no differences in age (Kruskal-Wallis test, P = 0.910) and gender (Fisher exact test, EON-pRNFL versus healthy controls: P = 0.422; EON-macular versus healthy controls: P = 0.675) between the EON-pRNFL, EON-macular and healthy control cohorts. EON-pRNFL: Peripapillary retinal nerve fiber layer measurements of EON patients; EON-macular: macular measurements of EON patients.

macular area Figure 2A) to macular thickness was evaluated (Monteiro et al., 2012). Visual sensitivity loss in the six areas, corresponding to the inferonasal, inferotemporal, temporal, superotemporal, supranasal, and nasal pRNFL thickness according to a previously published map used in glaucoma studies, was evaluated by previously described methods (Garway-Heath et al., 2000) (Figure 2B). The average visual field sensitivity of 12 central points was calculated.

Statistical analysis
All statistical analyses were performed using SPSS 17.0 software (SPSS, Chicago, IL, USA). Cohort differences were analyzed by the Kruskal-Wallis test for age and the Fisher exact test of Chi-square tests for sex. To analyze the differences in OCT measurements between the EON and healthy control groups, two-sample t-test was performed. For the correlations between pRNFL thickness, macular measurements and visual field sensitivity, linear regression models (Pearson test) were used. P < 0.05 was considered statistically significant.

Results
Quantitative analysis of subjects
A total of 11 patients (22 eyes) with EON were enrolled in this study. Among them, three eyes were excluded: the OCT parameters of two eyes were detected by a time-domain OCT device, and the refractive error of one eye was more than ±6.00 diopters sphere. Therefore, there were 19 affected eyes in our study. As two eyes in an EON patient were excluded due to papillary edema, pRNFL thickness in 17 EON-affected eyes was analyzed. Seven of the eyes did not have records of visual field sensitivity due to poor vision. Only 10 eyes underwent evaluation for the correlations of pRNFL thickness loss and visual sensitivity loss. Three subjects and their six affected eyes did not have macular OCT parameters resulting in macular measurements of 13 eyes being included in the analysis. Additionally, 3 eyes did not have visual field sensitivity records; the macular OCT parameters of these 10 eyes were used to investigate correlation with corresponding visual field sensitivity (Figure 3). A total of 24 healthy participants (48 eyes) were recruited as controls in our study. There were no differences in age (Kruskal-Wallis test, P = 0.910) and gender (Fisher exact test, EON-pRNFL versus healthy controls: P = 0.422; EON-macular versus healthy controls: P = 0.565) between the EON-pRNFL, EON-macular and healthy controls cohorts (Table 1).

SD-OCT
The temporal quadrant of pRNFL thickness in EON-affected eyes was lower compared with that in healthy controls, and the difference was statistically significant (P = 0.002). In the three remaining quadrants, there were no statistical differences in pRNFL thickness between the EON patient and healthy control cohorts (Table 1; Figures 4, 5). The PT3 sector of pRNFL, which composes the papillomacular bundle, showed the most thinning (PT3: P = 0.000; Table 2).

Taking overall macular measurements, cube macular volume and CAMT (P = 0.043) in the EON-affected eyes decreased compared with that in healthy controls, but for cube macular volume the difference was not statistically significant (P = 0.075). For the nine sectors of macular thickness

Table 2 pRNFL (µm) measurements in EON patients and healthy controls

|                | EON          | Healthy controls |
|----------------|--------------|------------------|
| pRNFL Mean±SD  | 95.29±19.25  | 100.15±9.84      |
| Superior pRNFL | 126.06±28.50 | 126.61±17.71     |
| Nasal pRNFL    | 68.47±11.54  | 70.02±13.05      |
| Inferior pRNFL | 127.65±36.59 | 131.09±16.18     |
| Temporal pRNFL | 57.35±16.34  | 72.33±9.18       |

The pRNFL thickness for EON versus healthy controls eyes evaluated by two sample t-tests. **P < 0.01, vs. EON (EON group: n = 17; healthy control group: n = 48; two-sample t-test). EON: Ethambutol-induced optic neuropathy; pRNFL: peripapillary retinal nerve fiber layer.
Figure 1 The maps of optical coherence tomography measurements for pRNFL and macular thickness. (A) Representative scanning laser ophthalmoscopy image represented 3.4-mm circular scans for analysis of pRNFL thickness. (B) The two optic disc maps showed four quadrant sectors of the pRNFL in the right and left eyes (PS, PT, PN, and PI). (C) The two optic disc map showed 12-hour pRNFL thickness in the right and left eyes. (D) The two macular measurement maps showed nine sectors divided by three concentric circles, each with a diameter of 1 mm (center), 3 mm (inner), and 6 mm (outer) (inner superior sector (C1-S), inner nasal sector (C1-N), inner inferior sector (C1-I), inner temporal sector (C1-T), outer superior sector (C2-S), outer nasal sector (C2-N), outer inferior sector (C2-I), and outer temporal sector (C2-T)). pRNFL: Peripapillary retinal nerve fiber layer; ETDRS: Early Treatment Diabetic Retinopathy Study.

according to ETDRS, the four sectors of the inner circle (C1-S, C1-N, C1-I, and C1-T) and nasal sector of the outer circle (C2-N) decreased compared with healthy controls (Table 3). All these results indicated that the inner circle and outer nasal sectors containing primarily papillomacular bundle axons are thinner in the EON-affected eyes compared with healthy controls. Papillomacular bundle axons are susceptible to EON impairment.

Visual function test and OCT measurements
There were no correlations between visual acuity and macular measurements in the EON-affected eyes. There were no correlations between pRNFL thickness and the corresponding visual sensitivity loss detected globally within the six regions. In the impaired sectors of the macula, 12 central points of visual sensitivity loss were correlated to CAMT and C2-N (Figure 6). All these results indicated that the thinning of CAMT and C2-N thickness could predict the onset of EON.

Discussion
In the present study, the average and temporal quadrant of
Figure 3 Demographic map of patients with EON.

EON: Ethambutol-induced optic neuropathy; OCT: optical coherence tomography; RNFL: retinal nerve fiber layer.

Figure 6 Correlation between VFS loss and macular thickness in patients with ethambutol-induced optic neuropathy.

(A) Correlation analysis between VFS (dB) and average macular thickness (µm) ($r^2 = 0.87, P = 0.000$). (B) Correlation analysis between VFS (dB) and inner superior sector (C1-S) thickness (µm) ($r^2 = 0.11, P = 0.342$). (C) Correlation analysis between VFS (dB) and inner nasal sector (C1-N) thickness (µm) ($r^2 = 0.23, P = 0.164$). (D) Correlation analysis between VFS (dB) and inner inferior sector (C1-I) thickness (µm) ($r^2 = 0.29, P = 0.110$). (E) Correlation analysis between VFS (dB) and inner temporal sector (C1-T) thickness (µm) ($r^2 = 0.02, P = 0.714$). (F) Correlation analysis between VFS (dB) and outer nasal sector (C2-N) thickness (µm) ($r^2 = 0.50, P = 0.022$). Linear regression analysis: Pearson test; $n = 10$. CAMT: Cube average macular thickness; VFS: visual field sensitivity; C1-S: inner superior sector of macular thickness; C1-N: inner nasal sector of macular thickness; C1-I: inner inferior sector of macular thickness; C1-T: inner temporal sector of macular thickness; C2-N: outer nasal sector of macular thickness.

quadrants of pRNFL thickness in 20 EON-affected eyes were not thinner than those in age-matched eyes of healthy controls. These different outcomes may result from the smaller size of samples in these studies. However, these might imply
Table 3 Macular measurements in EON patients and healthy controls

|                | EON (Mean±SD) | Healthy controls (Mean±SD) | P  |
|----------------|--------------|----------------------------|----|
| CAMT (µm)      | 276.31±113.00 | 283.44±10.96*              | 0.043 |
| CMV (mm²)      | 9.89±0.42     | 10.12±0.40                 | 0.075 |
| CSMT (µm)      | 238.92±18.54  | 244.69±21.89               | 0.192 |
| C1-S (µm)      | 290.00±9.57   | 306.00±11.59               | 0.935 |
| C1-N (µm)      | 292.08±8.54   | 302.17±14.16**             | 0.000 |
| C1-I (µm)      | 292.46±10.44  | 307.21±15.63**             | 0.000 |
| C1-T (µm)      | 286.00±11.59  | 284.79±11.26               | 0.464 |
| C2-S (µm)      | 278.77±14.98  | 272.58±14.89               | 0.935 |
| C2-N (µm)      | 286.85±13.35  | 302.17±14.16**             | 0.003 |
| C2-I (µm)      | 273.00±20.58  | 272.58±14.89               | 0.935 |
| C2-T (µm)      | 259.85±11.83  | 266.92±11.79               | 0.060 |

*P < 0.05, **P < 0.01, vs EON (EON group: n = 17; healthy controls group: n = 48; two-sample t-test). EON: Ethambutol-induced optic neuropathy; CAMT: cube average macular thickness, which was the average retinal thickness within the diameter of a 6-mm circle in the macula; CMV: the cube macular volume containing the total macular retina within the diameter of a 6-mm circle; CSMT: central subfield macular thickness, which was the average macular fovea thickness within the diameter of a 1-mm circle; C1-S: the retinal thickness of the inner superior sector; C1-N: the retinal thickness of the inner nasal sector; C1-I: the retinal thickness of the inner inferior sector; C1-T: the retinal thickness of the inner temporal sector; C2-S: the retinal thickness of the outer superior sector; C2-N: the retinal thickness of the outer nasal sector; C2-I: the retinal thickness of the outer inferior sector; C2-T: the retinal thickness of the outer temporal sector.

that pRNFL is not the ideal model to represent axonal loss in optic neuropathy for it is easily disturbed by optic dysplasia, edema and refraction abnormality.

Macular thickness had already reduced in the early stage of EON. In the present study, overall average macular thickness and macular volume decreased in EON-affected eyes compared with healthy controls. Macular thickness began to decrease in the four sectors of the inner circle and in outer nasal sectors. These results could be explained by the following reasons: maculae are disturbed by individual differences; furthermore, up to 40% of macular volume consists of the ganglion cell layer (Papchenko et al., 2012). Therefore, the macular thickness can be a more sensitive measure of the impairment of optic nerve in EON eyes. Currently, there are no reports regarding morphological alterations of macular thickness and macular volume in EON-affected eyes by SD-OCT. However, the idea that the macula was more sensitive to EON impairment has been proved in EON animal models. Histopathology of the retina in monkeys with EON revealed single cell necrosis, decreased retinal ganglion cells in the parafovea and increased microglia cells in the RNFL (Zoumalan et al., 2005). Additionally, retinal ganglion cells are most dense in the macula and form a stratified multi-cellular layer within the six central degrees of the visual field. Because of the lack of large retinal vessel interferences in the macula area and smaller individual variances, compared with pRNFL thickness, macular thickness should be a sensitive marker to predict functional injury (Kinoshi et al., 2012), which is confirmed in our study.

Previous studies have demonstrated that visual threshold and retinal ganglion cell thickness in the macula appear to be more correlated with visual sensitivity loss in the macula than in the pRNFL in patients with glaucoma, optic neuritis and anterior ischemic optic neuropathy (Kardon, 2011; Schneider et al., 2013). In the present study, because EON primarily affects central fixation, we focused on evaluating the correlations between macular thickness loss and central visual sensitivity loss in EON eyes and found that the CAMT and C2-N thickness losses were correlated to the loss of central visual sensitivity. Measurement of these thicknesses by OCT, an established ophthalmological technique, would be a useful clinical tool in predicting the onset of EON. The timely discontinuing use of ethambutol can prevent further visual loss.

The present study evaluated the macular thickness injury and their correlations to visual sensitivity loss, and revealed that CAMT and C2-N thickness were optimal structural markers to predict the onset of EON. This is the first report of these findings and should prove a very useful method to detect early EON and avoid subsequent visual function loss in patients. However, due to the small number of EON subjects and individual differences of optic nerve and macular thickness detected by OCT, this conclusion needs to be confirmed using a larger sample and a longitudinal study would add to our understanding of controlling EON.

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