

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

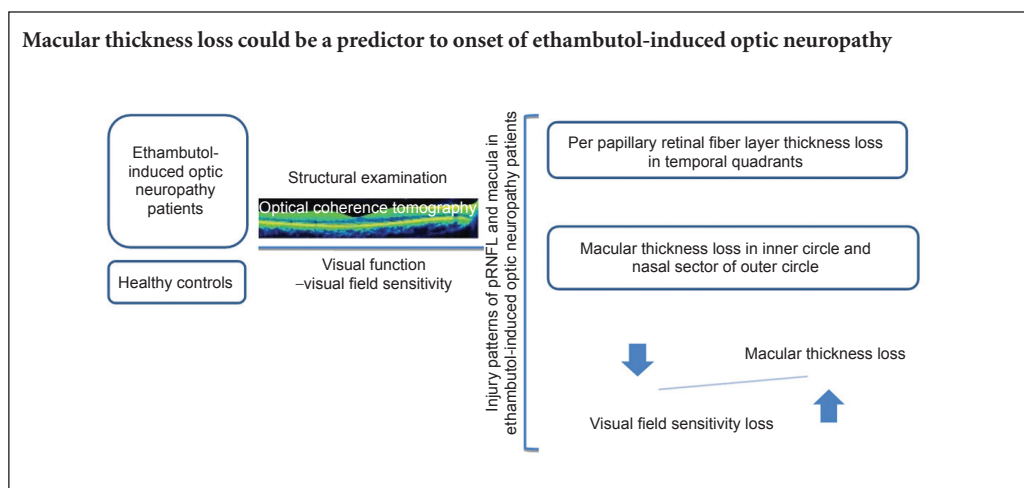
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## Graphical Abstract



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## 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 papillomacular 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  $\mu\text{m}$  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  $\mu\text{m}$  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; Garcia-Martin 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 anomalous) without other causes, bilateral central visual loss or cecentral scotomas; the secondary criteria: papillary pale and visual loss except for central or cecentral scotomas.

Exclusion criteria: refractive error greater than  $\pm 6.00$

diopeters sphere, an astigmatism of  $\pm 2.00$  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°), superonasal (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  $\times$  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 ( $\mu\text{m}$ ), macular volume, and nine sectors of macular thickness. The 3.4-mm circular scan model and standard Macular Cube model (512  $\times$  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
Min–Max	1–5	1–4	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, superonasal, 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

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

	EON		Healthy controls	
	Mean±SD	Min–Max	Mean±SD	Min–Max
Average pRNFL	95.29±19.25	58–132	100.15±9.84	81–129
Superior pRNFL	126.06±28.50	69–173	126.61±17.71	81–169
Nasal pRNFL	68.47±11.54	55–103	70.02±13.05	47–102
Inferior pRNFL	127.65±36.59	75–177	131.09±16.18	100–175
Temporal pRNFL	57.35±16.34	35–97	72.33±9.18**	53–103
PN1	114.47±30.69	73–177	116.76±22.60	52–168
PN2	86.65±16.14	65–122	85.26±19.73	51–138
PN3	58.59±7.83	49–80	57.74±11.06	35–86
PN4	65.00±16.83	43–110	66.54±15.95	41–103
PN5	106.06±27.68	59–155	107.28±23.76	70–168
P6	138.94±44.37	52–217	144.48±22.96	100–194
PT1	131.00±33.35	68–201	133.65±20.37	99–185
PT2	71.12±27.83	35–128	85.89±13.70	63–114
PT3	41.65±9.92	28–60	59.22±5.91**	47–72
PT4	58.41±19.59	36–108	72.02±15.23**	46–135
PT5	138.06±47.95	66–215	141.80±22.62	101–195
PT12	133.53±38.25	66–212	129.28±28.71	62–201

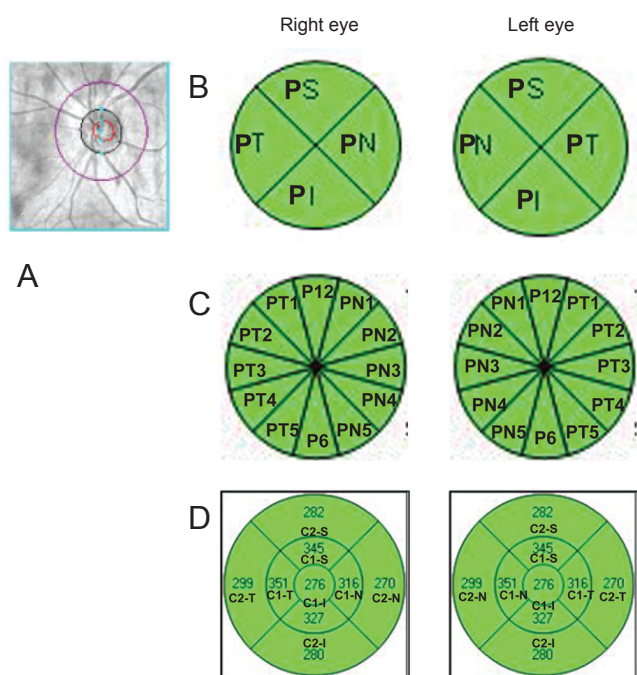
The pRNFL thickness for EON versus healthy controls eyes evaluated by two sample *t* tests. \*\* $P < 0.01$ , vs. EON (EON group:  $n = 17$ ; healthy control group:  $n = 48$ ; two-sample *t*-test). EON: Ethambutol-induced optic neuropathy; pRNFL: peripapillary retinal nerve fiber layer.

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



**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; PS: superior pRNFL; PT: temporal pRNFL; PN: nasal pRNFL; PI: inferior pRNFL.

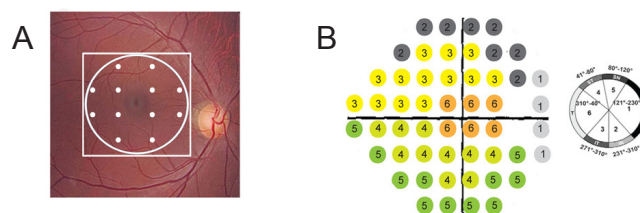
according to ETDRS, the four sectors of the inner circle (C1-S, C1-N, C1-I and C1-T) and nasal sector of the outer circle (C2-N) decreased compared with healthy controls (Table 3). All these results indicated that the inner circle and outer nasal sectors containing primarily papillomacular bundle axons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

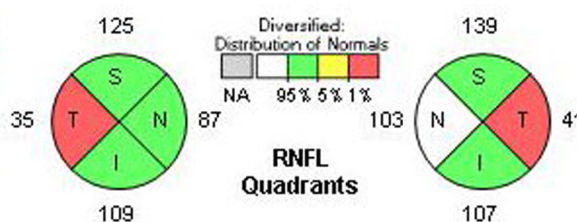
**Discussion**

In the present study, the average and temporal quadrant of



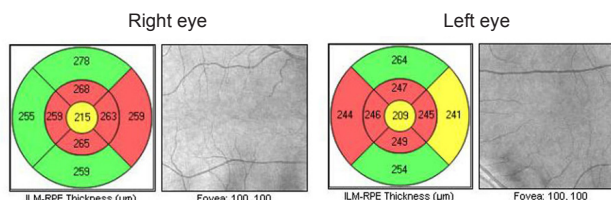
**Figure 2** The maps for macular thickness and pRNFL sectors thickness with corresponding VFS areas.

(A) The 12 points contained in the central circle correspond to the area circled in macular map. (B) The map showing the division of the 24 visual field test points and the optic nerve head into sectors according to published references (Garway-Heath et al., 2000; Monteirs et al., 2012). pRNFL: Peripapillary retinal nerve fiber layer; VFS: visual field sensitivity.



**Figure 4** pRNFL thickness alterations in EON patients and healthy controls.

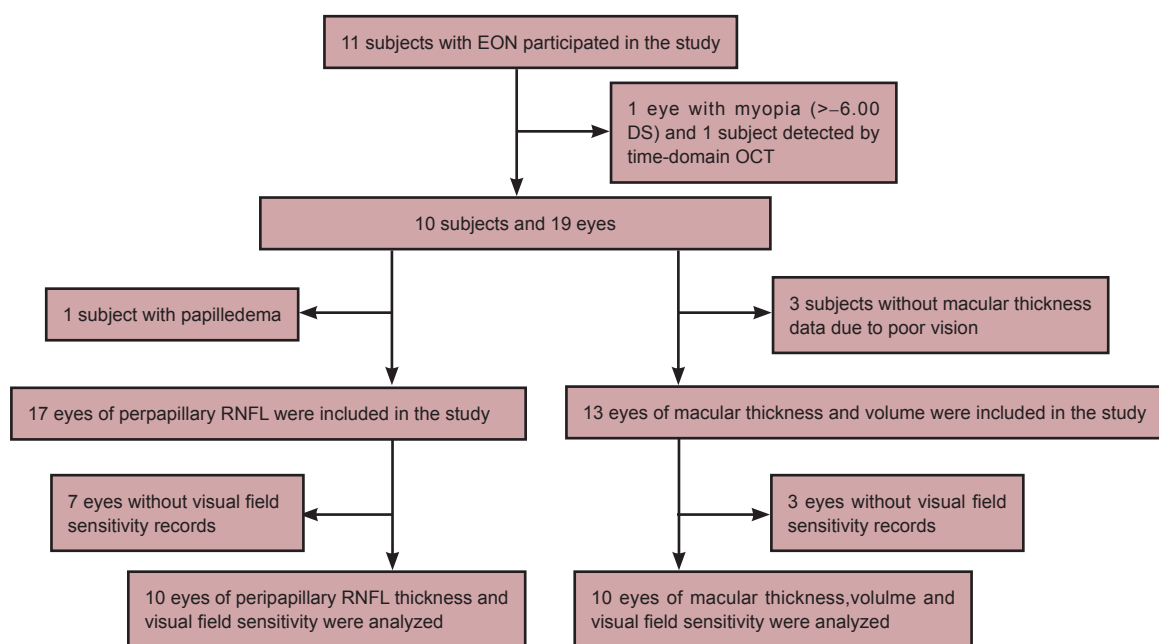
The quadrants of pRNFL thickness alterations detected by optical coherence tomography (The red areas in temporal quadrants in right and left eyes represented the thinning pRNFL areas in EON patients. S: Superior quadrant of pRNFL; N: nasal quadrant of pRNFL; I: inferior quadrant of pRNFL; T: temporal quadrant of pRNFL; pRNFL: peripapillary retinal nerve fiber layer; EON: ethambutol-induced optic neuropathy.



**Figure 5** Macular thickness alternations in nine sectors divided according to ETDRS between EON patients and healthy controls.

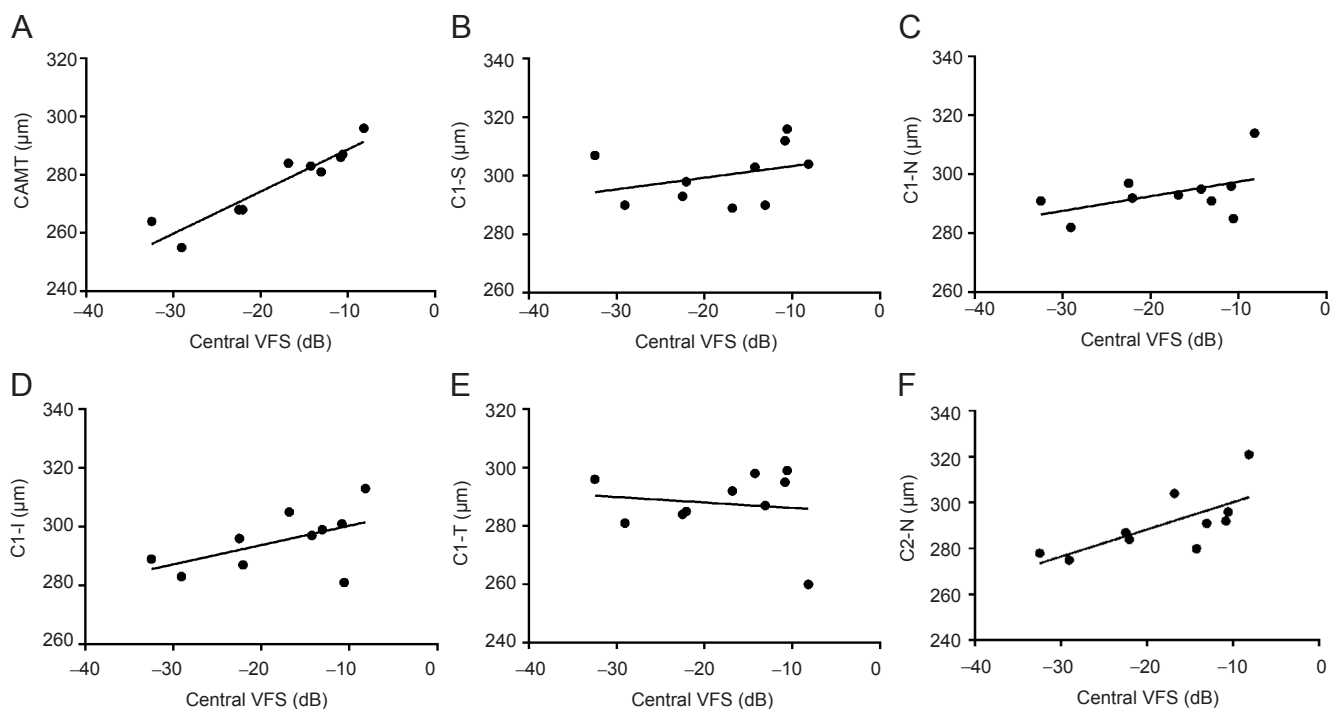
Macular thicknesses in the inner four sectors (red areas) and outer nasal sector (the red area in outer circle in right eye and yellow area in outer circle in left eye) in the EON-affected eyes are markedly reduced. The macular thickness in green areas was normal. EON: Ethambutol-induced optic neuropathy; ETDRS: Early Treatment Diabetic Retinopathy Study.

pRNFL thickness in patients with EON decreased. In particular, the temporal 3 clock sector (PT3) of pRNFL thickness, composed by the papillomacular bundle fibers, decreased sharply. These results were consistent with previous OCT studies concerning EON (Zoumalan et al., 2005; Chai et al., 2007; Menon et al., 2009). The thinning location of pRNFL coincided with that of papillomacular bundle fibers, which could prove that the papillomacular bundle is preferentially involved at a structural injury level in EON eyes. However, other studies have indicated that there was no axonal loss of pRNFL in EON eyes. Kim et al. (2008) showed that the average and four



**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 ( $\mu\text{m}$ ) ( $r^2 = 0.87$ ,  $P = 0.000$ ). (B) Correlation analysis between VFS (dB) and inner superior sector (C1-S) thickness ( $\mu\text{m}$ ) ( $r^2 = 0.11$ ,  $P = 0.342$ ). (C) Correlation analysis between VFS (dB) and inner nasal sector (C1-N) thickness ( $\mu\text{m}$ ) ( $r^2 = 0.23$ ,  $P = 0.164$ ). (D) Correlation analysis between VFS (dB) and inner inferior sector (C1-I) thickness ( $\mu\text{m}$ ) ( $r^2 = 0.29$ ,  $P = 0.110$ ). (E) Correlation analysis between VFS (dB) and inner temporal sector (C1-T) thickness ( $\mu\text{m}$ ) ( $r^2 = 0.02$ ,  $P = 0.714$ ). (F) Correlation analysis between VFS (dB) and outer nasal sector (C2-N) thickness ( $\mu\text{m}$ ) ( $r^2 = 0.50$ ,  $P = 0.022$ ). 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 con-

trols. 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		Healthy controls		P
	Mean±SD	Min–Max	Mean±SD	Min–Max	
CAMT (μm)	276.31±113.00	255–296	283.44±10.96*	264–311	0.043
CMV (mm <sup>3</sup> )	9.89±0.42	9.1–10.6	10.12±0.40	9.4–11.1	0.075
CSMT (μm)	238.92±18.54	216–274	24.69±21.89	213–295	0.192
C1-S (μm)	298.00±9.57	286–316	326.02±13.95**	298–348	0.000
C1-N (μm)	292.08±8.54	280–314	326.40±14.00**	281–354	0.000
C1-I (μm)	292.46±10.44	277–313	316.71±14.20**	281–354	0.000
C1-T (μm)	286.00±11.59	260–302	307.21±15.63**	253–344	0.000
C2-S (μm)	278.77±14.98	267–312	284.79±112.64	263–317	0.464
C2-N (μm)	288.85±13.35	269–321	302.17±14.16**	280–338	0.003
C2-I (μm)	273.00±20.58	239–321	272.58±14.89	248–313	0.935
C2-T (μm)	259.85±11.83	240–289	266.92±11.79	244–292	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 (Kinoshita 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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**Author contributions:** SHW obtained funding and supervision. CXP designed this study. CXP, BC, ADZ, BJY and QHW performed experiments. MY analyzed data. CXP wrote the paper. All authors approved the final version of the paper.

**Conflicts of interest:** None declared.

**Plagiarism check:** This paper was screened twice using Cross-Check to verify originality before publication.

**Peer review:** This paper was double-blinded and stringently reviewed by international expert reviewers.

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