

LITERATURE REVIEW

Diagnostic Value of Optical Coherence Tomography and Electroretinogram in Early Detection of Ethambutol-Induced Optic Neuropathy

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ABSTRACT

Background: Ethambutol-induced optic neuropathy (EON) is one of the most compelling adverse effect of tuberculosis treatment. Recovery often occur several months after treatment discontinuation. Unfortunately, some studies noted that nearly half of patients still have permanent visual loss. Early detection before clinical symptoms appear is necessary to prevent this devastating adverse effect. Therefore, this review aims to evaluate the diagnostic value of retinal nerve fiber layer (RNFL) thickness and ganglion cell inner plexiform layer (GCIPL) thickness changes with OCT, pattern and multifocal electroretinogram (ERG) changes during ethambutol treatment as early detection of EON.

Methods: A comprehensive search was conducted from electronic databases (PubMed, EBSCO, Google Scholar, and Springerlink) using relevant search terms. Articles from offline resources were also included. Included studies were selected based on predefined inclusion and exclusion criteria.

Result: Three studies reported significant thinning of RNFL after ethambutol initiation. Increased RNFL thickness in patients with EON and subclinical EON found in 3 studies. Significant macular GCIPL thinning was noted in 1 study. One study reported shortening of P50 implicit time and reduced N95 wave amplitude in pattern ERG.

Conclusion: Macular GCIPL thinning suggested to be the first pathological changes detected on patients with ethambutol treatment. It can be concomitant with thickening of peripapillary RNFL and followed by peripapillary RNFL thinning. Pattern ERG may reveal abnormality due to retinal ganglion cell (RGC) dysfunction before RGC loss.

Keyword: ocular coherence tomography, electroretinography, and ethambutol optic neuropathy.

INTRODUCTION

Tuberculosis is still one of the leading causes of single infectious disease and the top 10 causes of death

worldwide. South-East Asia is the highest rank among WHO regions (44%) and Indonesia is the third country after India

and China as the high TB burden countries (8%, 27%, and 9% respectively).¹

The wide use of ethambutol as a first-line agent and an important component in multidrug tuberculosis treatment is not without any risk of toxicity. This drug alters only the small caliber papillomacular bundle axons, yet the clinical findings will not be manifested until the fibers are lost.² The ocular symptoms may develop months after the initiation of therapy. It may become subclinical in the early stage, and vary among patients.³

The incidence of EON was stated in a review that 22.5 in 1000 persons receiving a standard dose of ethambutol for up to nine months suffered from visual impairment and 2.3 in 1000 had a permanent impairment.⁴ Several studies have shown that the incidence of EON is 1-5% as the common adverse effect.^{5,6}

The visual function alteration related to ethambutol use is often recovered several months after discontinuation of the treatment. But unfortunately, some studies report that 40-50% of patients experienced permanent visual loss even after the ethambutol stoppage.^{7,8} The funduscopy finding are relatively normal at the initial stage of the disease.⁵ To detect early anatomical changes before clinical manifestation, a quantitative objective marker is needed as a routine examination.

Ocular coherence tomography (OCT) has been used to analyze anatomical changes of peripapillary retinal nerve fiber layer (RNFL) as the involvement of retinal ganglion cells in EON patients. Ocular toxicity at the ganglion cell level can be detected with pattern electroretinogram (pERG) and functional damage at the level of cone cells can be detected with multifocal electroretinogram (mfERG). Hence, these modalities may have potential diagnostic value in detecting EON.

METHODS

The literature search was conducted from online databases including PubMed, EBSCO, Google Scholar, and Springerlink

using various combinations related to the relevant article "ocular coherence tomography, electroretinography, and ethambutol optic neuropathy". We also included articles from offline resources. Only articles were written in English and Indonesian were included. The search also limited to articles with the human subject. Reference lists from the selected articles were checked for potentially relevant studies.

The included articles were screened by reviewing abstracts to obtained the articles related to the aim of this literature review. The related complete studies were checked based on the inclusion and exclusion criteria. Inclusion criteria were all studies reported the changes of RNFL thickness using OCT and the result of the electroretinogram of patients on ethambutol therapy that met the aim of this review. Exclusion criteria were studies in non-human subjects, articles that could not be fully accessed, articles published not written in English or Indonesian.

All studies that met inclusion and exclusion criteria were rated based on levels of evidence developed by the Oxford Center for Evidence-based Medicine Levels of Evidence. All data extracted from selected articles that meet inclusion and exclusion criteria, including author, year of publication, study design, total subjects (eyes), retinal nerve fiber layer thickness, retinal ganglion cell layer, or ganglion cell inner plexiform layer at baseline or control and after ethambutol therapy were started. The data of electroretinogram results were also extracted.

RESULTS

The initial search yielded 20 articles. After screening the abstract, articles with relevant studies were reviewed. Ten articles met the inclusion criteria. Clinical course of study eyes were summarized in **Table 1**. There was 8 articles evaluated OCT changes and only 2 studies related to ERG changes in patients taking ethambutol treatment.

Gumus et al¹⁵ reported significant thinning in the average and superior quadrant RNFLs of the right eyes and thinning in superior and inferior quadrant RNFLs of the left eye at two months treatment period. Teng et al¹¹ found thinning of temporal quadrant RNFL thickness. And Significant thinning of peripapillary RNFL thickness two months after treatment was also found in Dialika et al⁹ study, but not clinically significant. Meanwhile, Significant thickening of mean temporal RNFL thickness was observed at six months in Jin et al¹⁰ study. Han et al¹³ study and Kim & Park's¹² study also proved an increase in retinal nerve fiber layer thickness. Lee et al⁶ found a significant difference in average and all quadrants macular GCIPL thickness between EON and control groups ($p < 0.001$). (See **Table 2**)

Table 1. Clinical course of study eyes and ethambutol (ETM) dosage

Author	Number of eyes (patients)	Time of follow up	Eyes developed EON/ Subclinical	The onset of EON/ Subclinical EON (months)	ETM dosage (mg/kg/day)
Jin et al ¹⁰	168 (84)	Baseline, every month & month after stoppage	None/22	N/A	14.72 ± 3.07
Lee et al ⁶	28(15)	Within 7 weeks of visual disturbances	28/None	N/A	N/A
Teng et al ¹¹	23(12)	Within 6 months after clinical onset	23/None	N/A	0.658 ± 0.201 (0.25-1) g/day
Kim & Park ¹²	62(31)	Baseline, 1, 2, 3, 4 & 6 months after initiation. 21 patients were followed 3,6 and 12 months after stopping ethambutol treatment	None/21 patients	6 months after ethambutol stoppage	15-19
Han et al ¹³	(37)	Baseline, 4 & 6 months after initiation of EMB	2 eyes of 1 patient/None	3	15-20
Kim & Hwang ¹⁴	20(10)	Within 4 months after visual loss	20/None	7.15 ± 3.64	N/A
Gumus et al ¹⁵	(20)	Baseline, 2 months after initiation of EMB	None	-	15
Dialika et al ⁹	58(29)	Baseline, 2 months after initiation of EMB	2 eyes of 2 patients/None	N/A	16.44 ± 2.7
Prakoso et al ¹⁶	40(20)	Baseline, 1 & 2 months after initiation	None	-	15-20
Kakisu et al ¹⁷	12(6)	N/A	12(6)	N/A	N/A

In Prakoso et al¹⁶ study pattern ERG showed a statistically shorten of P50 implicit time and statistically reduced N95 waves amplitude after two months follow up. There were no statistically significant changes in both N1 and P1 on multifocal ERG. Pattern ERG had earlier changes compare to multifocal ERG. Kakisu et al¹⁷

found the mean amplitude of pattern ERG decreased significantly. (see **Table 3**)

Table 2. Optical coherence tomography results

No	Author	Δ RNFL thickness					
		Average	Superior	Inferior	Temporal	Nasal	
1.	Jin et al ¹⁰	Baseline - 6 months	4.12	4.78	5.98	3.95 (p=0.014)	1.27
2.	Lee et al ⁶	Control - EON					
		RNFL	-0.85	-4.7	-1.2	7.2	-4.4
		GCIPL	-10.2 (p<0.001) Minimum -17.2 (p<0.001)	-11.2 (p<0.001)	-11.6 (p<0.001)	Superotemporal -5.9 (p<0.001) Inferotemporal -8.9 (p<0.001)	Superonasal -11.6 (p<0.001) Inferonasal -12.3 (p<0.001)
3.	Teng et al ¹¹	Control - EON					
		RNFL	-5.38	-2.8	-4.3	-15.55 (p<0.001)	-0.05
		RGCL	-20.16 (p<0.001)	-20.39 (p<0.001)	-19.78 (p<0.001)	Inferotemporal -16.21 (p<0.001)	Superonasal -23.92 (p<0.001) Inferonasal -24.22 (p<0.001)
4.	Kim & Park ¹²	Baseline - 6 months	8.02 (p=0.032)	-1.2	4.89 (p<0.001)	3.32 (p=0.029)	0.85
5.	Han et al ¹³	Baseline - 3 months (1 patient with visual problem)					
		RNFL	36.38 p<0.05	28.5 p<0.05	17 p<0.05	77 p<0.05	23 p<0.05
		GCIPL	-43.5 p<0.05	-46.5 p<0.05	-47 p<0.05	Superotemporal -52 p<0.05 Inferotemporal -57 p<0.05	Superonasal -34.5 p<0.05 Inferonasal -27 p<0.05
6.	Kim & Hwang ¹⁴	Control - EON	-2.75	-3.93	-5.42	2.78	-5.57
7.	Gumus et al ¹⁵	Baseline - 2 months					
		Right eye	-3 (p=0.024)	-8 (p=0.006)	-3	-1	3
		Left eye	-4 (p=0.001)	-4 (p=0.008)	-8 (p<0.001)	1	-5
8.	Dialika et al ⁹	Baseline - 2 months	-4.12 (p=0.001)	-6 (p=0.001)	-2	-3	-4 (p=0.045)

Table 3. Electroretinogram results

No	Authors	Electroretinogram			
		mS	□V	mS	□V
1.	Prakoso et al ¹⁶	Baseline - 2 months			
		Δ N1	Δ P1		
		mERG	0.28	-76.06	-0.85 -141.18
		Δ P50	Δ N95		
		pERG	-1.95 (p=0.049)	-0.42	-1.96 -0.93 (p=0.038)
2.	Kakisu et al ¹⁷	Normal eyes - follow up			
		pERG	-1.4	-1.3 (p<0.005)	N/A N/A

DISCUSSION

Changes in RNFL in several patients receiving ethambutol treatment were observed in most of all reviewed studies despite the standard dose of ethambutol as the WHO recommendation. Only Lee et al⁶ and Kim and Hwang's¹⁴ study showed no significant changes in RNFL thickness. Nonetheless, there was a relative thickening of temporal quadrant RNFL in the patients which might represent a mild swelling of the papillomacular bundle in Kim and Hwang's study.

Ethambutol-induced optic neuropathy occurred in one patient among 37 patients in Han et al¹³ study. They noted the thickening of the temporal sector of

peripapillary RNFL thickness and thinning in the perifoveal GCIPL thickness at the onset of symptoms. Unfortunately, this examination was performed after the onset of symptoms as the aim of our review was to see the early anatomical changes before clinical manifestation. Nevertheless, these findings suggest that the pathophysiology of ethambutol-induced optic neuropathy primarily involves retinal ganglion cells in the macular region and thinning of retinal ganglion cell bodies in the macula and axonal swelling in the peripapillary region may be early signs of this EON. As was found in Teng et al¹¹ study, whereas thinning of RGCL both in Leber's hereditary optic neuropathy (LHON) and EON occurred with similar patterns.¹⁸ Previous studies have mentioned the same condition in inherited mitochondrial optic neuropathy.^{19,20}

The study above is quite similar to Lee et al⁶ study, macular GCIPLs were significantly thinning. However, no significant changes of peripapillary thickness compare to the control group were observed. The peripapillary RNFL thickness may be normal or swollen in patients with EON. This study also found the nasal quadrant macular RNFL has a higher diagnostic ability than in temporal quadrant macular GCIPL. It can be associated with the vulnerability of the papillomacular bundle which is consisted of small-caliber parvocellular neurons. Nonetheless, the results of this study revealed every temporal quadrant macular GCIPLs also sensitive, thus ocular toxicity is not limited to the papillomacular bundle. This coincides with VF defect patterns that were observed demonstrating ocular toxicity is not functionally and structurally limited to the papillomacular bundle. Lee et al⁶ also noticed that the minimum macular GCIPL thickness afforded the highest diagnostic ability among all macular GCIPL parameters in patients with early EON.¹⁸ As seen in other studies, that minimum macular GCIPL thickness was the most sensitive among all macular

GCIPL parameters in the diagnosis of glaucoma and brain lesions.^{20,21}

Other than Han et al¹³ study, Jin et al and Kim and Park study also reported an increase in RNFL thickness on OCT. Jin et al¹⁰ assessed 22 eyes of 14 patients with subclinical ethambutol-induced optic neuropathy. Temporal RNFL revealed a post-administration increase at six months. However, VF testing can provide useful information because it is not clear whether structural change occurs in advance of a functional defect. The VFI showed a significant decrease at 3 months follow up. (see table 3.3) Both VF and OCT results were suggested more sensitive to detect subtle changes.¹⁰ Similarly, Kim and Park's¹² study revealed significant post-administration increases in temporal and inferior RNFL thickness at five months.¹⁶ None of the patients in these two aforementioned studies had a diminution of vision, changes in color vision or contrast sensitivity, consistent with Menon et al.²² In contrary, Salmon et al²³ reported diminished contrast sensitivity in patients receiving ethambutol treatment (38.2% at 3 months and 36.7% at 6 months). These clinical manifestations may appear after imminent clinical toxicity.

Gumus and Oner¹⁵ found a significant reduction in RNFL thickness after two months of treatment both in right and left eyes in terms of average and superior quadrant RNFL thickness. And significant RNFL thinning in inferior quadrant of left eyes. Chai et al²⁴ and Zoumalan et al²⁵ proved a substantial reduction in RNFL thickness temporal quadrant. However, both studies measured RNFL thickness at clinical presentation. And they had too small sample size. Teng et al¹¹ found thinning of temporal quadrant RNFL thickness similar to Chai et al²⁴ and Zoumalan et al²⁵ studies. This study compared RNFL thickness with age-matched healthy control. Dialika et al⁹ also found similar findings, there was significant thinning in quadrant superior, nasal and average RNFL after two months treatment.⁹

The different findings of these studies may be related to the timing of measurement along the course of pathological changes. Thinning of RNFL thickness may occur after the clinical diagnosis of EON as found in Yong-Kyu Kim and Hwang's²⁶ study. It may not be found in early-stage or subclinical EON. Mitochondrial disturbance due to ethambutol causes energy level depletion for axonal transport, particularly occur in papillomacular bundle's small-caliber axons (parvo-cellular RGC axons) at the early stage before ganglion cell apoptosis. The swelling can be observed, as reported in vitro LHON mimicking mice model. This may explain the thickening before thinning of RNFL thickness.²⁷ The wide age range of the patients included in these studies should be noticed, as the probable loss of a large number of axons or about 7500 (0.625%) axon loss each year after the age of 50.¹¹ Furthermore, in studies comparing RNFL between EON and control groups, the results may not show the actual decrease of RNFL due to ethambutol treatment.

Only one study had a large number of samples. Three studies compared the OCT examination between healthy control and patients who already diagnosed with EON. The time they evaluated the RNFL, GCIPL or RGCL was varied. Those may result in the conclusion of this review. Most of the studies did not mention the mean duration between the initiation of medication and the onset of subclinical EON/ EON.

The length of these studies can correlate with the variation results. Regular evaluation with a long-term follow up is needed to be performed to see the effect of ethambutol treatment since the clinical manifestation of EON may be seen even after the treatment stoppage. As was stated in Jin et al¹⁰ that the longer medication duration was suggested to be a strong risk factor for the occurrence of subclinical toxicity.

Prakoso et al¹⁶ reported a significant reduction of P50 wave implicit time and N95 wave amplitude after two months of ethambutol treatment. P50 wave results from an electrical signal sent to ganglion cell (as an outer retinal layer function) and the N95 wave is a result of electrical signal response transmitted from RGCs (record ganglion cell activities).²⁸ N95 wave is a component that reflects the RGCs layer and related directly to the RGCs volume. It is more sensitive to disfunction or early damage of ganglion cells.¹⁶ Kakisu et al¹⁷ reported a reduction of average N95 wave amplitude after clinical manifestation presented. The aforementioned study showed no significant changes in N1 and P1 waves on the mfERG examination. It may due to the ganglion cell damage is first occurred before cone cells and bipolar cells damage. The short-term follow up may play a role in this result.¹⁶

Prakoso et al¹⁶ suggested that a decrease in pattern ERG amplitude not only relates to ganglion cell loss but associated with retinal ganglion cell dysfunction. The articles that evaluate the ERG changes in patients taking ethambutol is still lacking. A future prospective study with a large number of samples is needed to compare both modalities.

CONCLUSION

In conclusion, OCT and ERG offer promising diagnostic modalities to detect early anatomical or electrophysiological of retina changes in a patient taking ethambutol treatment before clinical manifestation occurs. The findings in OCT may relate to the pathological course of ethambutol ocular toxicity. Macular GCIPL thinning suggested to be the first pathological changes detected on patients with ethambutol treatment. It can be concomitant with thickening of peripapillary RNFL and followed by peripapillary RNFL thinning. Pattern ERG may reveal abnormality due to retinal ganglion cell dysfunction before retinal

ganglion cell loss. However, further study with a long-term prospective study with serial OCT and ERG in a large number of samples is needed.

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