

Scanning Laser Polarimetry in Pulmonary Tuberculosis Patients on Chemotherapy

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Abstract

Introduction: The aim of this study was to analyse the thickness of the retinal nerve fibre layer (RNFL) of pulmonary tuberculosis patients on ethambutol and isoniazid. **Materials and Methods:** This was a prospective cohort study where patients with newly diagnosed pulmonary tuberculosis requiring chemotherapy, including ethambutol and isoniazid, were imaged using scanning laser polarimetry. Their mean baseline RNFL thickness and various scanning laser polarimetry parameters of both eyes were measured 2 weeks after the commencement of chemotherapy. The measurements were repeated at 3 months and 6 months after treatment. The various parameters of the baseline and the follow-up measurements were compared using paired sample *t*-test with Bonferroni correction. **Results:** Twenty-four patients (16 males and 8 females; mean age, 51.0 ± 17.6 years) were recruited. There was no statistically significant difference between the baseline and the follow-up measurements in RNFL thickness and all other scanning laser polarimetry parameters. **Conclusion:** In this cohort of subjects, there was no subclinical change in RNFL thickness detected by scanning laser polarimetry in pulmonary tuberculosis patients on chemotherapy, including ethambutol and isoniazid, after 6 months of treatment.

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Key words: Drug toxicity, Ethambutol, Isoniazid, Lasers, Optic diseases, Retina, Tuberculosis

Introduction

Pulmonary tuberculosis is a worldwide disease. In Hong Kong, there are about 7000 new cases of pulmonary tuberculosis each year and the prevalence remains high at about 110/100,000.^{1,2} The male elderly (>60 years) are at the greatest risk.³ The consensus treatment regime in Hong Kong consists of a 6-month multi-drug course of chemotherapy under directly observed treatment (DOTS).⁴ The recommended regime in the treatment of uncomplicated pulmonary tuberculosis cases comprises 2 months' treatment with isoniazid, rifampicin, pyrazinamide together with streptomycin or ethambutol, followed by 4 months of isoniazid and rifampicin.

Although chemotherapy is highly effective, it has its own risks. Ethambutol and isoniazid have been associated with toxic optic neuropathy.⁵ Although this ocular complication is relatively uncommon, the toxic effect can be severe and

irreversible. Even with the prompt cessation of ethambutol, visual recovery is expected in only half of the patients. In the older age group, only one-fifth of patients experienced visual improvement.⁶ Apart from clear verbal instruction to patients to cease medications once visual symptoms occur, the current preventive measure is to perform regular ophthalmological assessment. Toxic optic neuropathy is diagnosed clinically when patients present with deteriorating vision, impaired colour vision and visual field changes.⁷ Nevertheless, a significant portion of patients with ethambutol-related toxic optic neuropathy still suffers from permanent poor visual outcome followed by optic atrophy.⁸ In order to achieve earlier detection of toxic optic neuropathy, the use of electrophysiological tests, such as visual evoked potential (VEP), have been studied in human subjects.⁹ In 6 of the 14 patients taking ethambutol, subclinical changes in the latency and amplitude of the P100 component in pattern reversal VEP were demonstrated

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after 1 to 3 months of treatment. These changes were reversed in only half of the patients after the cessation of treatment. Based on this finding, early detection of any subclinical change in retinal nerve fibre layer (RNFL) thickness may be useful for earlier detection of ethambutol-related optic neuropathy, before optic atrophy occurs. In a recent study, detectable changes in peripapillary RNFL thickness were documented in 3 patients with known history of ethambutol-induced optic neuropathy by the use of optical coherence tomography.¹⁰ However, subclinical structural changes in RNFL thickness have not been studied in clinically asymptomatic human subjects receiving ethambutol and isoniazid.

Various new technologies have evolved over the recent decade to investigate RNFL, including scanning laser polarimetry (SLP) and optical coherence tomography. The nerve fibre analyser (NFA) is a confocal scanning laser ophthalmoscope with an integrated polarimeter that indirectly assesses the thickness of the RNFL objectively based on retardation of polarised light due to the birefringent properties of microtubules of the nerve fibres.¹¹ It has been used for quantitative measurement of RNFL thickness in patients with ocular hypertension and primary open-angle glaucoma.¹²⁻¹⁵ As the measurement procedure is fast and objective, it is ideal for elderly patients who find the visual field test difficult. This study is focused on the detection of subclinical RNFL thinning using the NFA in pulmonary tuberculosis patients on the standard chemotherapy regime.

Materials and Methods

This was a prospective cohort study in which the RNFL measurements of patients who had been under treatment for pulmonary tuberculosis were documented in subsequent follow-up sessions. Ethambutol-induced optic neuropathy was defined clinically by unexplained decrease in vision, colour vision impairment, abnormal fundal examination or visual field abnormality in patients receiving ethambutol.

Between May 2001 and November 2002, all patients with newly diagnosed pulmonary tuberculosis requiring standard recommended chemotherapy, including both ethambutol (15 mg/kg to 25 mg/kg) and isoniazid (5 mg/kg), were recruited from the Department of Medicine, Heaven of Hope Hospital. Patients with pre-existing optic nerve diseases, retinopathy of all causes, previous ocular trauma, glaucoma, operation or laser procedure as well as those taking concurrent, potentially neurotoxic medications e.g., amiodarone, were excluded from the study to avoid their confounding effects on RNFL measurements.

A protocol of standardised ophthalmological assessment, which was approved by the Ethics Committees of the Chinese University of Hong Kong and the United Christian

Hospital, was performed on each subject. An informed consent form was signed by every studied patient.

Recruited subjects had their baseline RNFL thickness measured using the GDx NFA (Laser Diagnostic Technologies, Inc, San Diego, CA, USA) 2 weeks after the commencement of chemotherapy. This time point was chosen for the baseline measurement because the contagion of mycobacterium tuberculosis is rapidly lowered after the commencement of chemotherapy and optic neuropathy seldom occurs within 2 weeks of treatment. Moreover, in one study involving 13 patients having ethambutol-related toxicity, optic neuro-pathy developed 1 to 6 months (mean, 2.9) after starting treatment.¹⁶ Thus, we repeated RNFL measurement at 3 months after treatment in this study. Furthermore, since ethambutol toxicity is known to be dose-related, delayed toxicity is not expected after the cessation of treatment.¹⁷ RNFL measurement was therefore repeated at 6 months after treatment when all patients had completed their treatment.

Although variable corneal compensation that would eliminate incomplete compensation among those anterior segment outliers was not available in the GDx model used in this study, this is not a significant issue in this longitudinal comparative study design. Three pictures with passing grade of the image quality were taken for each eye. The one with the best image quality, as interpreted and quantified by the software (version 1.0.05) generated image quality table, together with the lack of motion artifacts as shown on the nerve fibre layer thickness map, was chosen for further analysis. An extended nerve fibre analysis table including various parameters was generated for each eye. The parameters for analysis include symmetry, superior ratio, inferior ratio, superior/nasal ratio, maximum modulation, ellipse modulation, the number, average thickness, ellipse average, superior average, inferior average and superior integral. During each follow-up, patients also had visual acuity test, intraocular pressure (IOP) measurement, slit-lamp and fundal examination and colour vision test (Ishihara plates) documented. Automated Humphrey threshold visual field test [C-24(2)] (Humphrey Field Analyzer HFA 750, Humphrey Instruments, Dublin, CA, USA) was also performed during each visit. Unreliable results, defined as fixation loss of >20% and/or false positive and/or false negative of >30%, were excluded.

All the examinations and investigations were mainly performed by one experienced operator. Upon completion of data collection over the 6-month period, the various parameters of the GDx NFA of the baseline and the follow-up measurements were compared using the paired sample *t*-test with Bonferroni correction. A *P* value of <0.05 was considered statistically significant.

Results

A total of 41 patients with newly diagnosed pulmonary tuberculosis who had been treated with the standard recommended chemotherapy regime were recruited. Among those subjects, 17 were excluded due to various reasons. These include defaulting follow-up over the 6-month study period (14 subjects), poor NFA image quality due to markedly tilted optic discs (1 subject) and cataract (1 eye of a subject), incidental finding of branch retinal vein occlusion (1 subject) and termination of ethambutol by physicians due to a subjective drop in vision (1 subject).

The recruited subjects all had normal optic disc, macula and baseline SLP scan findings. For the patient who complained of a subjective drop in vision, no optic neuropathy was diagnosed clinically upon regular follow-up, with stable visual acuity, normal colour perception and no visual field change. RNFL analysis performed at 3 months and 6 months after chemotherapy in this patient revealed no progressive change in any of the measured parameters either.

A total of 24 patients (47 eyes) completed the study. The ages of the 16 male and 8 female subjects ranged from 20 years to 78 years [mean, $51.0 \pm$ standard deviation (SD) 17.6]. Two recruited subjects had congenital red-green colour deficiency. The range of Snellen visual acuity, and the mean IOP, 2 weeks and 3 months after treatment was 0.2 to 1.0, and 14.0 mm Hg, respectively. After a 6-month period of treatment, their Snellen visual acuities ranged from 0.3 to 1.0 while the mean IOP was 13.6 mmHg. All subjects had normal IOP throughout the study.

Among the 24 subjects included, only 8 subjects produced reliable visual field results in all 3 measurements for

interpretation. Although visual field testing was repeated one more time during each measurement if the subject was noted to produce an unreliable result after the first attempt, 9 subjects in total still had unreliable visual field results in any one measurement while 7 subjects produced unreliable results due to unacceptable fixation loss. All of them had stable visual acuity and normal fundal examination. There was no newly detected colour vision impairment. None of the studied subjects developed toxic optic neuropathy clinically throughout the study period. By comparing the average of various parameters of NFA taken at 2 weeks, 3 months and 6 months after treatment by paired sample *t*-test with Bonferroni correction (Table 1), no statistically significant change was found in any of the NFA parameters over the 6-month period of study (Table 2).

Discussion

Although toxic optic neuropathy caused by ethambutol is rare, it is unpredictable, potentially severe and sometimes irreversible. The neurotoxic effect of isoniazid may be attributed to a relative pyridoxine deficiency but the exact pathophysiological mechanism of ethambutol-related toxic optic neuropathy remains unclear. However, the specific toxicity of ethambutol to rodent retinal ganglion cell via an excitotoxic pathway has been demonstrated in an animal study.¹⁸ Changes in P100 latency and amplitude of pattern VEP were also noted in clinically asymptomatic human subjects treated with ethambutol. Although pattern VEP may be useful for detecting early changes in ethambutol-related optic neuropathy, this electrophysiological test is time-consuming, requires good patient cooperation and dedicated investigative technique. Similarly, visual field tests also require good patient concentration and

Table 1. GDx Measurements at Various Time Points during Anti-tuberculosis Treatment

NFA parameters	Mean \pm SD		
	Baseline	3 months post-treatment	6 months post-treatment
Symmetry	1.00 \pm 0.14	1.00 \pm 0.15	1.01 \pm 0.16
Superior ratio	2.01 \pm 0.58	2.04 \pm 0.53	2.03 \pm 0.53
Inferior ratio	2.01 \pm 0.52	2.06 \pm 0.52	2.04 \pm 0.54
Superior/Nasal ratio	1.79 \pm 0.43	1.78 \pm 0.45	1.80 \pm 0.48
Maximum modulation	1.26 \pm 0.49	1.29 \pm 0.45	1.29 \pm 0.47
Ellipse modulation	2.43 \pm 0.61	2.54 \pm 0.68	2.55 \pm 0.75
Number	40.83 \pm 26.83	37.32 \pm 24.26	37.11 \pm 26.91
Average thickness	64.23 \pm 11.78	63.49 \pm 10.69	64.65 \pm 10.38
Ellipse average	66.32 \pm 13.08	66.47 \pm 11.21	67.06 \pm 11.47
Superior average	73.19 \pm 16.56	72.79 \pm 13.37	74.06 \pm 15.47
Inferior average	76.30 \pm 18.01	76.98 \pm 15.65	77.23 \pm 16.45
Superior integral	0.22 \pm 0.04	0.22 \pm 0.04	0.22 \pm 0.04

Baseline measurement: taken at 2 weeks after treatment

Table 2. *P* Values (with Bonferroni Correction) of GDx Measurement Changes at Various Time Points during Anti-tuberculosis Treatment

NFA parameters	<i>P</i> value (Two-tailed paired <i>t</i> -test)		
	Baseline - 2 nd measurements	2 nd - 3 rd measurements	Baseline - 3 rd measurements
Symmetry	2.808	2.574	2.355
Superior ratio	1.896	2.466	2.163
Inferior ratio	0.945	1.875	1.749
Superior/Nasal ratio	2.343	2.124	2.793
Maximum modulation	1.806	3.000	1.683
Ellipse modulation	0.831	2.589	0.594
Number	0.201	2.742	0.171
Average thickness	1.530	0.960	2.388
Ellipse average	2.715	1.731	1.686
Superior average	2.400	1.032	1.722
Inferior average	2.013	2.535	1.734
Superior integral	2.916	1.731	1.968

cooperation. This is also well demonstrated in this study, in which only one-third of all subjects produced reliable visual field results for diagnosing optic neuropathy. Since detectable changes in peripapillary RNFL thickness were reported in patients with known ethambutol-induced optic neuropathy by the use of optical coherence tomography, this study aims to investigate any subclinical changes in RNFL thickness by the use of scanning laser polarimetry in clinically asymptomatic patients. This investigation is more objective and less time-consuming compared to pattern VEP and automated perimetry. Its finding may be useful in detecting early ocular toxicity of ethambutol and also has an implication for the ocular safety of the current recommended chemotherapy regime for treating pulmonary tuberculosis.

This study allowed us to follow patients on ethambutol and isoniazid longitudinally for a period of 6 months. The problem with non-compliance to medications did not exist because the treatment regime uses a direct observation system to achieve 100% compliance. In this study, no significant change in RNFL thickness was demonstrated in any NFA parameter after a 6-month course of chemotherapy, including 2 months' treatment with ethambutol. Potential confounding factors affecting RNFL measurements, including pre-existing retinopathy or other optic neuropathy such as glaucoma, were excluded early in the study. Although it has been shown that there was positive correlation between the degree of cataract and RNFL measurements, which may mask any possible reduction in RNFL thickness, significant cataract progression was unlikely due to the relatively short period of study and stable visual acuity among the patients during serial follow-

up.¹⁹ To conclude, although prolonged latency and decreased amplitude has been shown in patients receiving ethambutol, no structural change in RNFL thickness suggestive of structural damage was detected in this study by the use of scanning laser polarimetry.

However, this study has certain limitations. First, the sample size is relatively small for investigating a relatively uncommon adverse RNFL drug-related effect. The small sample size may result in insufficient power of this study to detect structural change in RNFL thickness, especially if the changes are subtle. Moreover, the true pre-treatment RNFL measurement could not be obtained in this study because of the risk of the investigator contracting this highly infectious disease before commencement of chemotherapy among the patients. A 2-week post-treatment measurement was used as the baseline instead. Furthermore, any possible delayed structural change in RNFL thickness may have been missed as the RNFL measurement was completed at 6 months.

In conclusion, in patients receiving ethambutol and isoniazid without visual or colour vision impairment, scanning laser polarimetry did not show any structural change in the their RNFL thickness.

Proprietary Interest

GDx® is a registered trade mark of Laser Diagnostic Technologies, Inc (San Diego, CA, USA), in which the authors have no financial interest.

Competing Interest

The authors have no financial interest in the anti-tuberculosis drugs in this study.

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