Color vision defect in patients with tuberculosis receiving Ethambutol treatment

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Purpose: To evaluate the incidence of color vision defect in patients with tuberculosis receiving ethambutol (EMB) treatment and to evaluate the sensitivity of the two methods of color vision tests in detecting the color vision defect.

Materials and methods: The authors prospectively evaluated patients newly diagnosed with tuberculosis from the infectious diseases clinic at Thammasat Hospital, Pathum Thani, Thailand. The patients were enrolled from October 2018 to December 2019. The patients underwent complete eye examinations including optical coherence tomography (OCT) optic nerve analysis and visual field at their first visit. Color vision measured using the Ishihara Pseudo-isochromatic 17-plates and Farnsworth-Munsell D-15 test at initial visit and monthly were recorded. The patients were followed-up for at least 6 months or until they stopped EMB treatment.

Results: Twenty-seven patients (54 eyes) were included in the study. Thirteen were female and fourteen were male. They had a mean age of 49.8 ±17.6 years (range 22 to 77 years). The mean daily dose of ethambutol is 17.38 ±2.39 mg/ kg (range 13.6-21.8 mg/kg). Baseline color vision and monthly color vision was remained normal in all patients. After following up the patients for about 6 months after anti-tuberculous drugs were stopped, color vision remained normal in all patients using both color vision tests.

Conclusion: Although the present study did not find the incidence of color vision defects in our patients as predicted, the authors still emphasize the importance of color vision test screening in patients receiving EMB treatment because color vision defect may indicate early toxic optic neuropathy.

Keywords: Color vision, Tuberculosis, Ethambutol, Toxic optic neuropathy

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Introduction

Ethambutol (EMB) induced toxic optic neuropathy is one of the drug toxicities in patients receiving anti-tuberculous drugs that result in visual loss. EMB activates intracellular metal-containing enzymes such as zinc or copper-containing cytochrome oxidase which result in cell membrane damage.[1] The daily dose and the duration of drug administration affects drug accumulation and toxic optic neuropathy. No safe dose has been reported with EMB-induced toxic optic neuropathy was

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observed with doses as low as 12.3 mg/kg.[2] The mean duration of ocular toxic effects has been reported to be 3 to 5 months.[3] No study has reported with the onset of ocular toxicity after withdrawal of the drug. In a recent systematic review, Ezer N, et al. reported the cumulative incidence of any visual impairment in patients with active tuberculosis receiving EMB was 22.5 per 1000 cases. Here, 4.3 per 1,000 cases have been reported to have permanent vision loss. However, after analyzing only those who received an average dose of 27.5 mg/kg/day (MKD) or less and the duration treatment was about 2-9 months, the incidence of any visual impairment has been reduced to approximately 19.2 per 1,000 cases.[4]

EMB-induced toxic optic neuropathy has been classified with regards to its clinical manifestation into 2 types; axial and periaxial toxic effects. Patients with axial toxic effect usually present with decreased visual acuity, color vision defect or central scotoma field defect. Patients with periaxial toxic effect usually present with slightly decreased visual acuity, color vision defect or peripheral field defect.[5] Previous studies reported that changes in color vision can occur before visual acuity is decreased.[6,7] Therefore, color vision defect may be the earliest sign of ocular toxicity.

Wong JKW, et al. reported the Farnsworth-Munsell D-15 test appears to be more sensitive than the Ishihara Pseudo-isochromatic plates in detecting color vision defects as subjective screening tool for suspected EMB-induced toxic optic neuropathy.[8] In the present study, the primary outcome is to evaluate the relative incidence of color vision defect without having blurring vision by monthly follow-up during the course of anti-tuberculous drugs treatment. The secondary outcome is to evaluate the sensitivity of the two methods of color vision tests in detecting the color vision defect.

Material and methods

The study was approved by the Medical Ethics Committee of Thammasat University (MTU-EC-OP-2-183/61), Pathum Thani, Thailand, and was conducted in accordance with the tenets of the Declaration of Helsinki. The authors prospectively evaluated patients newly diagnosed with tuberculosis from the infectious diseases clinic at Thammasat Hospital. The patients were enrolled from October 2018 to December 2019. The inclusion criteria included subjects of either gender between the age of 20 to 70 years old, subjects who recently diagnosed pulmonary tuberculosis or extrapulmonary tuberculosis that have been started EMB within the first month of treatment and subjects can test both Ishihara color test and Farnsworth panel D-15 test. Subjects with congenital color vision defect, previous retina or optic nerve damage, best corrected visual acuity (BCVA) worse than 20/200, a history of drug use that may affect color vision such as Hydroxychloroquine and Amiodarone were excluded.

Demographic data (age, gender), details of anti-tuberculous drug treatment such as daily dosage, duration of treatment, and visual symptoms were collected. Baseline visual function included best corrected visual acuity (BCVA) on the Snellen chart, pupillary function, average retinal nerve fiber layer (RNFL) thickness, visual field, duration of follow-up, and results of color vision tests by

Ishihara Pseudo-isochromatic plates and Farnsworth-Munsell D-15 test. were collected. RNFL measurements were derived from a 200 × 200 cube optic disc scan using a Cirrus® HD OCT 4000 (Carl Zeiss, Meditec, Dublin, CA, USA). An abnormally thickened RNFL was reported when the thickness is greater than 99% of age-matched normal database. While thin RNFL was defined as thickness belonging to less than 1% of the age-matched normal database. Visual field measurements were derived from the 30-2 Swedish Interactive Thresholding Algorithm (SITA) full-threshold Humphrey visual field (HVF) (Carl Zeiss Meditec Inc., Dublin, CA). Pattern deviation represents focal depressed areas in the points tested when accounting for overall depression as estimated by the mean deviation plot. An abnormal visual field was reported when the localized defect that represented nerve fiber layer defect is detectable.

Study protocol

The patients underwent complete eye examinations included optical coherence tomography (OCT) optic nerve analysis and visual field at their first visit. Color vision measured using the Ishihara Pseudo-isochromatic 17-plates and Farnsworth-Munsell D-15 test at initial visit and monthly were recorded. The patients were followed-up for at least 6 months or until they stopped EMB treatment.

Ishihara Pseudo-isochromatic 17-plates test instruction; patients must identify the correct number, or correctly trace the wiggy lines in plates 1-17. Patients with color vision defect should be able to distinguish these. The correct answers of eight or more than is normal (score= 0). The correct answer of seven or less out of seven is abnormal (score = 1). Farnsworth-Munsell D-15 test instruction; patients must select the color cap which most closely matches the reference cap and placed in the bottom of the box and slide next to the reference cap. Patients then continue to select the next closest color disc and places each in sequence in the bottom of the box. The patient's selection of the caps is mapped on a color diagram template, evaluation determines color vision defects in deutan, protan or tritan axis discrimination. If the patient's selection order was reference cap,1, 2,3,4,5,6,7,8,9,10,11,12,13,14,15, the interpretation is normal (score = 0). For example, if the patient's selection order was reference cap, 1,15,2,3,14,13,12,11,10 ,9,8,7,6,5,4 the interpretation is abnormal (deutan pattern) (score =1). Patients with color vision defects were re-evaluated as described above. Internist will be notified when the authors suspect EMB-induced toxic optic neuropathy.

Statistical analysis

We analyzed the data with excel tables (Microsoft windows XP professional version 2002 service pack3) and the statistical analysis was performed with SPSS software version 14.0 (IBM Inc, Chicago, IL). Demographic data and other characteristics are described in terms of mean and range. Primary outcome was described in percentage. Secondary outcome was analyzed statistically by using chi-square-test and the *p-value* was obtained. A *p-value* of less than 0.05 indicated statistical significance.

Results

A total of 55 patients were enrolled in the study. Twenty-eight patients did not return to follow up after the first visit and were excluded from the final study. Thus, 27 patients (54 eyes) completed the number of follow ups and were included in the final study. Thirteen were female and fourteen were male. They had a mean age of 49.8 ±17.6 years (range 22 to 77 years). Twenty-four patients (88.9%) have pulmonary tuberculosis (TB), two patients (7.4%) have tuberculous lymphadenitis, and one patient

	Total (N=27)	
	Numbers	**Percentage**
Gender		
Female	13	48.2
Male	14	51.8
Etiologies of tuberculosis		
Pulmonary tuberculosis	24	88.9
Extrapulmonary tuberculosis	3	11.1
Ishihara Pseudo-isochromatic 17-plates		
Score = 0	24	100
Score = 1	0	0
Farnsworth-Munsell D-15 test		
Score = 0	24	100
Score = 1	0	0

Table 1. The numbers and percentage of patients' demographic data, etiologies, and color vision score tests

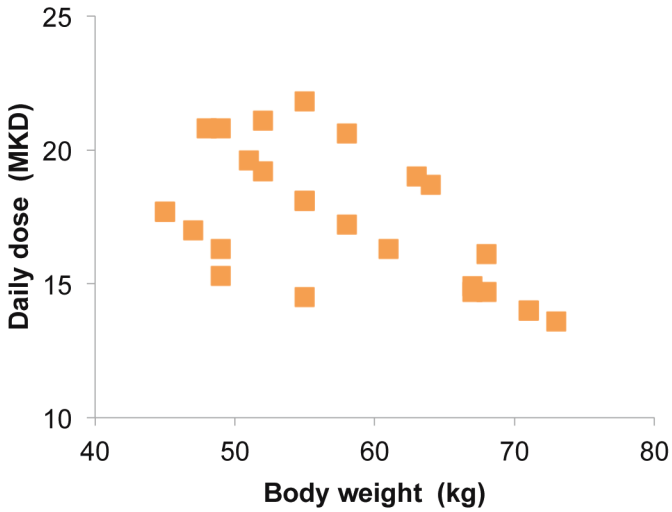

Figure 1 Graph plotting shows the daily dosage of EMB in each patient based on body weight.

(3.7%) has shoulder joint tuberculosis. The mean daily dose of EMB is 17.38 ±2.39 MKD (range 13.6-21.8 MKD). At the first visit, the visual acuity ranged from 20/20 (log minimum angle of resolution; log MAR 0.0) to 20/200 (log MAR 1), with a mean acuity of 0.15 ±0.19 log MAR. Slit-lamp examination, fundus examination, OCT optic nerve analysis, and visual field were all normal at their first visit.Table 1 summarizes the demographic data and the clinical profiles of the patients. Figure 1 shows the daily dosage of EMB in each patient based on body weight.

Baseline color vision and monthly color vision remained normal in all patients. After following up the patients for at least 6 months or until they stopped EMB treatment, color vision remained normal in all patients using both color vision tests. No patient had any color abnormalities in the color vision test in one method without any abnormalities in the other method.

Discussion

Tan et al. reported the incidence of EMB-induced toxic optic neuropathy varies between 15% in patients receiving EMB 50 MKD, 5% with 25 MKD, and less than 1% with 15 MKD.[9] Trusiewicz et al. stated that red-green color defects were the most common and early defect in asymptomatic patients.[10] In Thailand, the recommended daily dose of EMB from the national tuberculosis program guideline is 15-20 MKD. Melamud et al. reported onset of EMB-induced toxic optic neuropathy varies between 3 to 5 months and does not develop until at least 1.5 months after EMB treatment.[3] In previous studies; Kaimbo KW, et al. reported the incidence of color vision defect without decreased visual acuity in 42 patients with tuberculosis receiving EMB was 36%.[12] Cruz EM, et al. reported the incidence of color vision defect without decreased visual acuity in 64 patients with tuberculosis receiving EMB was 47.88%.[13]

In the present study, the patients received an average daily dose of 17.38 ±2.39 MKD (range 13.6-21.8 MKD) and the duration lasting from 6-9 months, which is a safety dose for our patients. Because the patient has a baseline complete eye examination since the beginning of receiving EMB. Moreover, baseline OCT optic nerve analysis and visual field are objective tests confirming that they had normal optic nerve function. If during the study, patients develop color vision defect, it will help to confirm that color vision defect may be the result of ocular toxicity. Majority of our patients with pulmonary tuberculosis are currently treated with a sixmonth combination of drugs that include isoniazid, rifampicin, ethambutol, and pyrazinamide for two months, followed by isoniazid and rifampicin without ethambutol for four months. Visual loss rarely occurs before the patient has been receiving the drug for at least 2 months. No study has reported onset after withdrawal of drug, the authors then monitor the patients until the treatment is complete. If there is no color vision defect, the authors do not continue to monitor. Therefore, majority of our patients received EMB for about 2 months, but the patients were followed up until at least 6 months or until they stopped EMB treatment. Therefore, although the patients in the study had not been monitored for at least 9 months as in the previous study, they were thought to have obtained relevant data

to the results. Comorbidity such as diabetes, hypertension, renal disease, tobacco/alcohol-induced toxic optic neuropathy is associated with an increased risk of pre-existing optic nerve damage. Although the authors did not exclude patients with comorbidity of EMB-induced toxic optic neuropathy such as diabetes, hypertension, and renal disease in the exclusion criteria, none of the patients had underlying disease. This may be another reason why the authors did not find the incidence at all.

Previous studies reported the Farnsworth-Munsell D-15 test appears to be more sensitive than the Ishihara Pseudo-isochromatic plates in detecting color vision defects in EMB-induced toxic optic neuropathy.[5] Since no patient included in the present study developed color vision defects, the authors cannot compare the sensitivity of the two methods of color vision tests in detecting the color vision defect. The limitation of the study is the small sample size. Although this is a prospective study, many patients were lost to follow up o and some patients died due to other reasons during the follow-up period. This study requires further evaluation with larger sample sizes before its results can be recommended for the multidisciplinary care for patients.

In conclusion, although the present study did not find the incidence of color vision defect in patients with tuberculosis receiving EMB treatment like other studies have predicted, the authors still emphasize the importance of color vision test screening in patients receiving EMB treatment because color vision defect may indicate early toxic optic neuropathy.

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All authors report no conflicts of interest relevant to this article.

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