

Ethambutol-Induced Optic Neuropathy in Patients of Tuberculosis

Zulfiqar Ali¹, Nadia Nazir¹, Soufia Farrukh¹, Muhammad Javaid Iqbal¹, Imran Nazir² and Zunaira Alvi²

ABSTRACT

Objective: To find out characteristics of patients having ethambutol-induced optic neuropathy (EON) at a tertiary care hospital of South Punjab, Pakistan.

Study Design: Observational Study

Place and Duration of Study: This study was conducted at the Outpatient Department of Ophthalmology, Bahawal Victoria Hospital, Bahawalpur from January 2018 to December 2019.

Materials and Methods: During the study period, a total of 35 patients were enrolled with visual impairment following initiation of ethambutol usage and diagnosed as EON. All patients had decreased visual acuity, impairment of color vision by "Ishihara color plate", or had abnormal results of visual field and/or flash and pattern visual evoked potential examination. Basic ophthalmologic evaluations like visual acuity, color vision as well as optic disc evaluation were done. Gender, age, medical history, date of diagnosis, treatment, visual acuity, color vision and slit lamp bio microscopy were recorded for all patients.

Results: Out of a total of 35 patients, 23 (65.7%) were male and 12 (34.3%) female. Most of the patients, 24 (68.6%) belonged to rural areas of residence while 11 (32.4%) from urban areas. In terms of types of tuberculosis, 34 (97.1%) were having pulmonary tuberculosis. Majority of the patients, 28 (80.0%) were over 60 years of age while mean age was noted to be 66.34 years with standard deviation of 10.81 years. Visual acuity loss was observed at 6.42±3.94 months following initiation of ethambutol treatment. Among 19 (54.3%) patients, visual acuity decline was bilaterally symmetric.

Conclusion: Ethambutol-induced optic neuropathy is a major concern during anti-tubercular treatment. Timely detection and withdrawal of ethambutol along with prompt treatment and monitoring by ophthalmologists should be done.

Key Words: Ethambutol, optic neuropathy, tuberculosis, visual impairment

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INTRODUCTION

Tuberculosis (TB) is considered a major systemic infection globally.¹ Treatment of TB consists of combination of anti-TB drugs. Ethambutol has been in use for the treatment of TB since 1960s and ethambutol linked visual impairment was identified soon following its introduction.² Ethambutol is among the 1st line anti-TB drugs utilized. In the past, each anti-TB drug was given individually according to weight of the TB patient but now days, fixed-dose combination (FDC) are available and have made it much more convenient

for the patients to take these drugs in a single pill usually.³

Ethambutol can cause toxicity while most commonly observed adverse effects of ethambutol include diminished visual acuity, rash and fever.^{4,5} Ethambutol-induced optic neuropathy (EON) is a well-known ocular complication and could progress in to permanent visual loss. Some studies have estimated the incidence of EON which is found to be between 1-1.5%.⁶⁻⁸ EON has been found to correlate with the ethambutol dosage.⁹ The exact mechanism behind EON is not fully known but it could be attributed to ethambutol and its metabolite which have zinc chelating effects that cause dysregulation of the retinal hemostasis.⁶ Ethambutol is thought to interfere with iron containing complex-I and copper containing complex-IV so might disrupt the oxidative phosphorylation and produce reactive oxygen species that might lead to retinal ganglion cell damage.^{5,10} No study has been done in Pakistan to find out the characteristics of the patients having of EON. Most of the studies conducted globally consist of case reports and small case series. So, the current study aimed to find out characteristics of patients having EON at a tertiary care hospital of South Punjab, Pakistan.

¹. Department of Ophthalmology, Bahawal Victoria Hospital, Quaid e Azam Medical College, Bahawalpur.

². Bahawal Victoria Hospital, Bahawalpur.

Correspondence: Dr. Zulfiqar Ali, Assistant Professor, Ophthalmology Department, Bahawal Victoria Hospital, Quaid e Azam Medical College, Bahawalpur, Pakistan
Contact No: 0300-9689475
Email: dr.zulfiqarali64@hotmail.com

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MATERIALS AND METHODS

This observational study was done at the Outpatient Department of Ophthalmology, Bahawal Victoria Hospital, Bahawalpur from January 2018 to December 2019. During the study period, a total of 35 patients were enrolled with visual impairment following initiation of ethambutol usage and diagnosed as EON. All patients had decreased visual acuity, impairment of color vision by "Ishihara color plate", or had abnormal results of visual field and/or flash and pattern visual evoked potential examination. All patients having other eye related disorders/diseases like cataract, retinal diseases, glaucoma, or any other reason of optic neuropathy were not enrolled. Informed consent was taken from all study participants. Approval from "Institutional Ethical Committee" was also acquired.

Basic ophthalmologic evaluations like visual acuity, color vision as well as optic disc evaluation were done. A special proforma was designed to record all the study information. Gender, age, medical history, date of diagnosis, treatment, visual acuity, color vision and slit lamp bio microscopy were recorded for all patients. Quantitative data was expressed as mean and standard deviation while qualitative data was represented as frequency and percentages. SPSS version 26.0 was used for all data handling and analysis.

RESULTS

Out of a total of 35 patients, 23 (65.7%) were male and 12 (34.3%) female. Most of the patients, 24 (68.6%) belonged to rural areas of residence while 11 (32.4%) from urban areas. In terms of types of tuberculosis, 34 (97.1%) were having pulmonary tuberculosis. Majority of the patients, 28 (80.0%) were over 60 years of age while mean age was noted to be 66.34 years with standard deviation of 10.81 years. Table 1 is showing characteristics of patients having EON in the present study. Visual acuity loss was observed at 6.42±3.94 months following initiation of ethambutol treatment. Among 19 (54.3%) patients, visual acuity decline was bilaterally symmetric.

Table No.1: Characteristics of Patients having Ethambutol-induced Optic Neuropathy

| Characteristics | Mean±SD |
|---|-----------------|
| Age (years) | 66.34±10.81 |
| Weight (kg) | 56.17±9.48 |
| Duration of Ethambutol Treatment (months) | 6.42±3.94 |
| Ethambutol cumulative Dosage (mg/kg) | 2727.24±2047.84 |
| Initial VA logMAR | 0.84±0.67 |
| Initial color (Ishihara color test) | 7.18±8.44 |

DISCUSSION

The incidence of EON is estimated to be between 1-1.5% in various studies conducted globally.⁶⁻⁸ Ezer N

et al in their meta-analysis evaluating studies involving TB patients treated with ethambutol from 1965-2011 noted incidence of visual impairment as 22.5 per 1,000 cases while permanent visual impairment was noted in 2.3 per 1,000 cases who had received ethambutol treatment in standard dosage for up to 9 months.¹¹ The actual burden of EON could be much higher if we consider that not all patients are reporting or referred to ophthalmology clinics so EON might get overlooked among TB patients getting ethambutol treatment.

In the present study, mean duration of ethambutol treatment (months) at the time of visit to ophthalmology clinic by the patients was noted to be 6.42±3.94 months whereas mean ethambutol cumulative Dosage (mg/kg) was noted to be 2727.24±2047.84 mg/kg. Chen S et al from Taiwan¹² evaluating 62 cases EON noted mean duration of ethambutol treatment at the time of EON diagnosis to be 5.94±4.1 months which is close to what we noted in the present study. Lee EJ et al⁸ evaluating patients of EON noted visual loss at a mean duration of 7.31±9.45 months after initiation of ethambutol. As present research was an observational study and we did not have any plans of recording follow up data of the patients, various authors have reported that visual functional recover after discontinuation of the ethambutol treatment in many of the cases. Chen S et al from Taiwan¹² noted 50% of their patients having EON and visual impairment to recover after discontinuing ethambutol treatment. Kumar A et al¹³ analyzing 7 consecutive patients with EON and severe visual impairments noted that 42.3% of them had visual recovery after a mean follow up 8.3±2.1 months. Lim SA⁶ analyzing 3 EON cases noted that 1 case had recovery from visual impairment after discontinuation of ethambutol treatment while remaining 2 had mild visual improvements after stopping ethambutol treatment. Some researchers have found incidence of EON to have relation with daily dose and duration of treatment of ethambutol.^{14,15} It has also been seen that cases who developed EON have significantly higher daily ethambutol when compared to those cases who did not develop EON.⁸ Ethambutol is known to get rapid absorption while most part of ethambutol is excreted out through urine, it is vital to adjust the dosage of ethambutol as per creatinine clearance.¹⁶ Some clinicians have also proposed that patients having renal impairment should not be treated with ethambutol as ethambutol might be causing toxicity in these cases. We were unable to record renal functions in our cases but studies have found out significantly decreased glomerular filtration rate (GFR) in cases that developed EON.⁸ Patients having decreased renal functions should be monitored carefully by the clinicians when they are under treatment with ethambutol.

Ethambutol toxicity is thought to affect the small-caliber papillomacular bundle axons while it is also observed that optic disc pallor does not exist up until

months following loss of fibers.¹⁷⁻¹⁹ Clinical signs of EON might absent in many of the patients during fundus examination whereas around half of EON cases might have already develop optic disc pallor at the actual time of EON diagnosis. Methods like electrophysiological testing for the screening of EON could be helpful. Multi-focal electroretinogram is also a useful tool for the diagnosis and monitoring of EON.²⁰

Our study had few limitations as well. As this was a single center study, the findings of this study cannot be generalized. Further studies involving large sample size, multiple population sets and centers will further add to what is known about the spectrum of EON. We were unable to record the incidence of EON so further studies could be planned to enroll TB patients under treatment with ethambutol.

CONCLUSION

Ethambutol induced optic neuropathy is a major concern during anti-tubercular treatment. Ethambutol induced optic neuropathy can lead to visual impairments and permanent vision loss. Timely detection and withdrawal of ethambutol along with prompt treatment and monitoring by ophthalmologists should be done. Patients planned to receive anti-tubercular treatment can be referred to ophthalmologists for pretreatment evaluation.

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Author's Contribution:

Concept & Design of Study: Zulfiqar Ali
 Drafting: Nadia Nazir, Soufia Farrukh
 Data Analysis: Muhammad Javaid Iqbal, Imran Nazir, Zunaira Alvi
 Revisiting Critically: Zulfiqar Ali, Nadia Nazir
 Final Approval of version: Zulfiqar Ali

Conflict of Interest: The study has no conflict of interest to declare by any author.

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