International Journal of Research and Review
Vol.7; Issue: 2; February 2020
Website: www.ijrrjournal.com
Case Report *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Ethambutol Induced Optic Neuropathy: A Rare Case Report

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ABSTRACT

Ethambutol (EMB) is one of the first-line drugs in the treatment of tuberculosis. Ethambutol-induced optic neuropathy (EON) is a very well known side effect which is either dose or duration related. The ocular manifestations of EON include painless loss of central vision and cecocentral scotomas in the visual field. We report a rare case of EMB-induced optic neuritis in a 19 year old female, who was on ATT for spinal tuberculosis for 3 months. Patient presented with painless diminution of vision in both eyes for 15 days which was not improving on refraction. Patient was diagnosed as a case of EON on series of ophthalmic examination and ethambutol was stopped immediately. Patient was given some neurotrophic drugs for 1 month. After 1 month, patient had BCVA of 6/9 in both eyes. Fundus and visual fields were also within normal limits except mild temporal disc pallor.

Keywords: Ethambutol, Optic neuritis.

INTRODUCTION

Tuberculosis is one of the most important systemic infections around the world. It is caused by Mycobacterium tuberculosis and more common in developing countries.[1] Ethambutol is a first-line medication that is used in the treatment of tuberculosis. However, it can lead to side effects including problems with vision, liver problems and allergies.[2] Ethambutol-induced optic neuropathy (EON) is a well-known complication arising from the use of ethambutol, the severity of which is in a dose-dependent manner. The clinical characteristics of EON include painless loss of central vision and cecocentral scotomas in the visual field. Incidence of EON in different countries is close to 1%.[3] The exact mechanism of action of ethambutol is unknown; however, it has been hypothesized that it acts as a chelating agent that disrupts one of the several metal-containing enzyme systems in the nucleic acid structures of mycobacteria.[4] Its toxicity involves the same mechanism. Early animal experiments showed that ethambutol causes lesions in the optic chiasm and optic nerves.[5] Classically described as dose- and duration-related and reversible on therapy discontinuation, reversibility of optic neuritis always remains controversial. Unfortunately, patient education and immediate cessation of the drug do not always change the final visual outcome. The toxicity appears unpredictable, and therefore the drug should be used cautiously.

Ethambutol causes optic neuropathy in 1-5% of patients who were on ATT.[6] The dosage of 25mg/kg/day for 2 months should be reduced to 15 mg/kg/day maintenance dose which is considered safe as well as effective, although toxicity has been reported below this dosage too.[7] The visual symptoms usually start 2–8 months after the drug is started. Leibold described two types of ocular neuritis due to the therapy of EMB, i.e., axial neuritis and periaxial neuritis. Axial neuritis is the most common

form which involves the papillomacular fibers of optic pathway and ensuing in decline of visual insight, color vision impairment and central scotomas. Periaxial neuritis peripheral defects are noted, but insight is spared.[8] Normally the neuritis is retrobulbar, and the fundus is normal. Dyschromatopsia may be the earliest sign of toxicity, and blue-yellow color changes are the most common.[6] Cecocentral scotomas are the common visual field defect, but bitemporal defects and peripheral field constriction have also been reported.[3] Pupillary abnormalities can be subtle, and visual evoked potential may be needed to confirm the diagnosis. Contrast sensitivity measurement has also been found effective in detecting subclinical toxicity.[9] Optical coherence tomography (OCT), which is now commonly used to measure nerve fiber layer thickness in patients with glaucoma, can also be used to quantify such changes in ethambutol toxicity. It can quantify the loss of retinal nerve fibers of these patients as a sign of early toxicity, before the fundus changes become apparent. OCT, therefore, is an additional objective test to monitor patients on ethambutol, especially when used in conjunction with visual fields.[10] International guidelines on prevention and early detection of ethambutol-induced ocular toxicity have been published. Other than stopping the drug, no specific treatment is available for the optic neuropathy caused by ethambutol. Once this is accomplished, many patients will recover, and this may take weeks to months. However, there are reports that vision may still decline or fail to recover even when the drug is stopped if damage is severe enough.[8]

CASE REPORT

A 19 year old female, weighing 49kg, came to Regional Institute of Ophthalmology PGIMS Rohtak with complaint of diminution of vision for 10 days. She was on Category 1 ATT (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin) for spinal tuberculosis for past 3 months. Dosage of ethambutol given to her was 25mg/kg for 2 months and then reduced to 15mg/kg. She was not having any family history of neuropathy.

We performed series of ophthalmic examinations to see the severity of her ocular condition. Her BCVA (best-corrected visual acuity) was 6/18 (OD) and 6/60 (OS) respectively. IOP (intraocular pressure) was 12 mm Hg in Right eye and 14 mm Hg in Left eye by Goldmann Applanation Tonometry (GAT). The slit-lamp microscope examination of bilateral anterior segments was absolutely within normal limits (Figure 1&2). The pupils were normal with no relative afferent pupillary defect (RAPD). Colour vision was impaired with greater impairment of red/green hue discrimination.

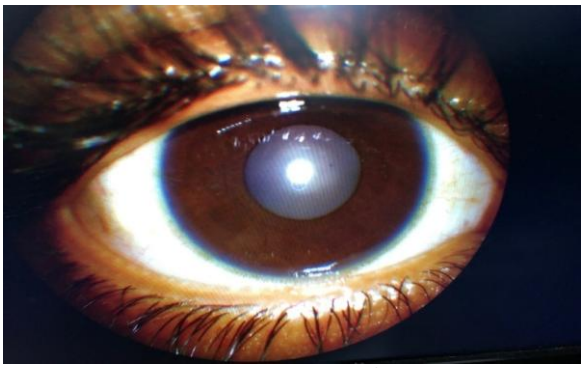

Figure 1: Anterior segment of Right Eye

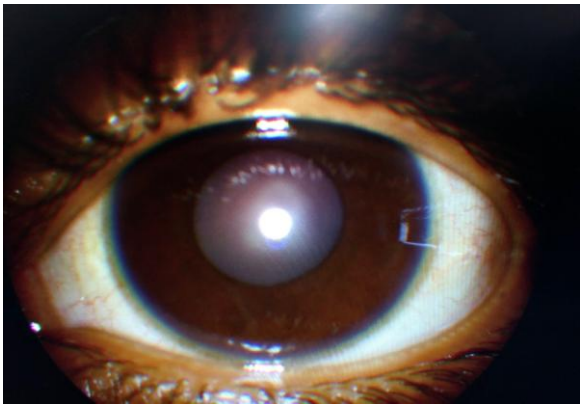

Figure 2: Anterior Segment of Left Eye

The fundus examination indicated swollen hyperaemic disc with blurring of disc margins in both eyes (L>R) with normal foveal reflex. (Fig 3&4).

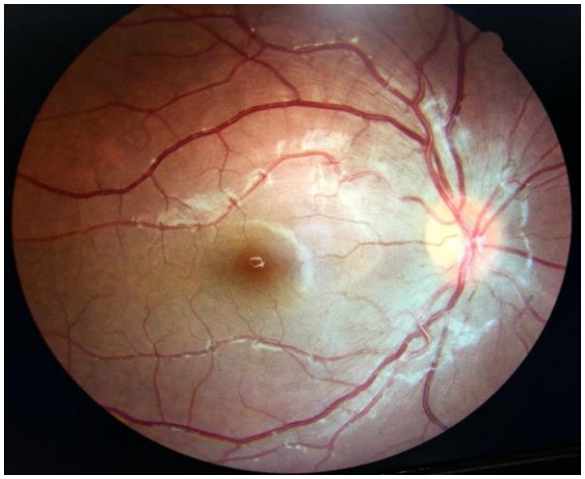

Figure 3: Right Eye Fundus Photograph showing disc hyperaemia and blurred margins

Automated perimetry by Humphrey Field Analyzer indicated typical cecocentral visual field defects in both eyes (L>R) (Fig. 5&6). Based on the ocular examinations listed above, this patient was diagnosed as EON.

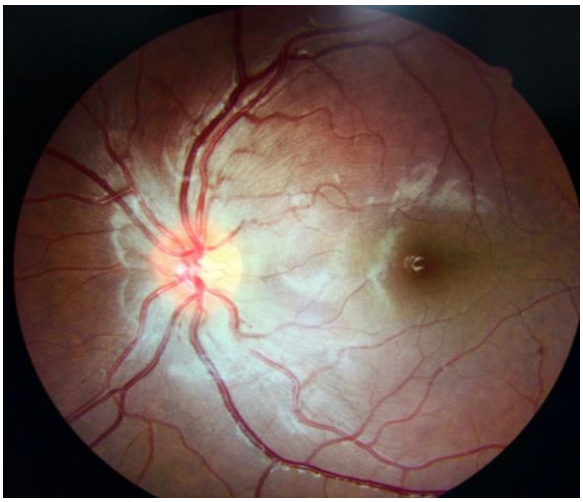

Figure 4: Left Eye Fundus Photograph showing hyperaemic disc with blurred margins

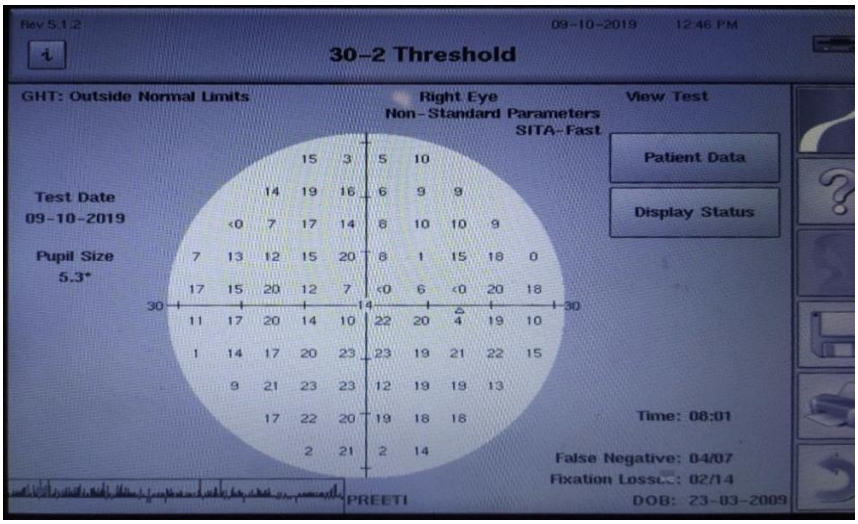

Figure 5: HFA 30'-2 of R/E

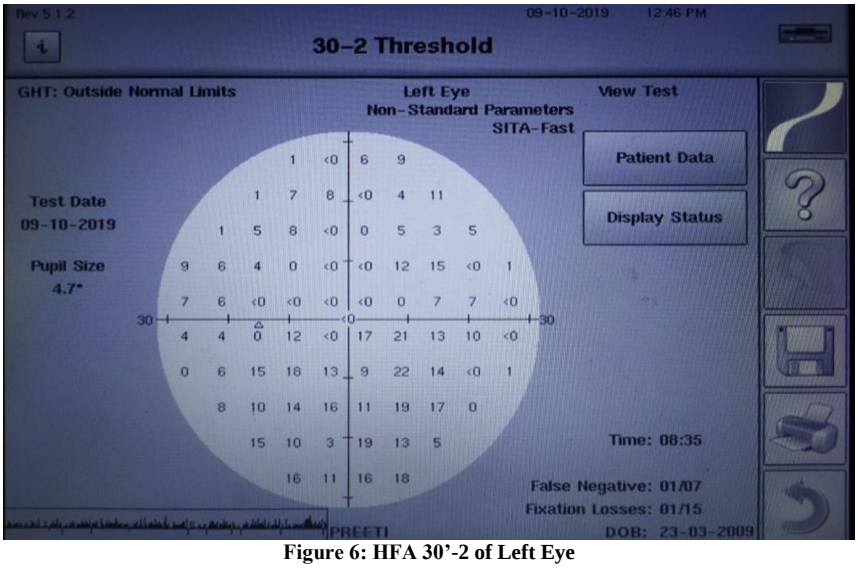

Figure 6: HFA 30'-2 of Left Eye

Patient was asked to stop ethambutol immediately and was given neurotrophic drugs for 1 month. She was reviewed again after 1 month. Her BCVA was 6/9 in both eyes. Colour vision was also found to be normal. On fundus examination, optic disc of both eyes was well defined with sharp margins and mild temporal disc pallor. (Figure 7&8). On perimetry, there was no scotoma this time.

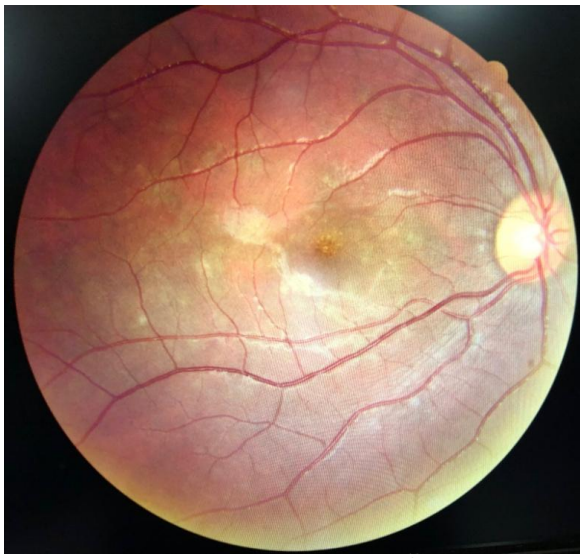

Fig 7: Right eye Fundus Photograph after 1 month

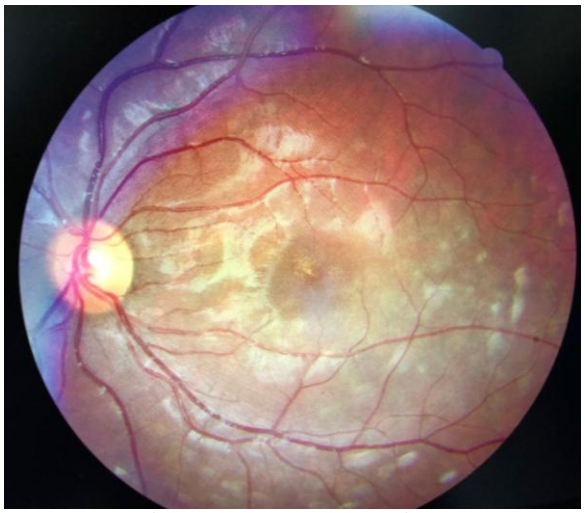

Fig 8: Left eye Fundus Photograph after 1 month

DISCUSSION

The overall incidence of ethambutol-induced optic neuropathy in tuberculosis cases receiving ethambutol was about 1% that is correlated to the dosage. Among the patients who received ethambutol at dose as low as 12.3 mg/mg/day, some still represented ocular ethambutol toxicity.[9] However, among the patients receiving high dosage of 15 to 25 mg/kg/day of the drug that was close to the case presented above, the reported incidence was up to 5% to 6% when taking for at least 2 months.[10] Therefore, there is no safe dose for ethambutol in the clinical practice. The ocular toxicity should be monitored closely during the therapies and short after the stoppage, especially for the ones that are taking high dosage.

The onset time of EON is not predicable. The ocular symptoms develop from a few days to 2 years after the initiation of drug use.[11] This patient showed typical cecocentral scotomas, which was common among majority of the patient. Fundus examination showed swollen and hyperaemic disc because of early presentation. Our patient fully recovered because of early detection and young age, which are good prognostic factors. In some severe cases, the automated perimetry examination indicated bitemporal hemianopia, which may resulted from involvement of optic chiasm in the development of ethambutol-induced optic neuropathy.[12,13]

It is still controversial that whether EON is reversible or not. Early studies indicated some of the ethambutol-induced vision impairments were irreversible, which included visual field defects and contrast sensitivity deterioration.[5] However, much more research works demonstrated reversal of the toxicity induced by ethambutol after 1 month of stoppage of the drug in majority of the patients.[13] The reported recovery rate among the patients who stopped taking the drug for more than 1 month was around 50%.[5] The prognostic factors for EON may be related to patients age. Tsai and Lee demonstrated that only 1 out of 5 patients aged >60 year-old got recovered, but 4 out of 5 patients aged <60 year-old got recovered. Reversibility of the toxicity can be indicated by conventional ophthalmic examinations, including visual acuity, colour vision, and visual field.[14]

CONCLUSION

As per WHO statistics in 2011, India is highest TB burden country with an incidence of 2.2 million cases out of 9.6 million cases worldwide. So all tuberculosis patients who are put on ATT, especially Ethambutol, must be sent for regular ophthalmic examination and they must be educated by its side effects i.e. vision loss, loss of contrast sensitivity, colour vision impairment etc.

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How to cite this article: Monika, Kumar J, Rathi M et.al. Ethambutol induced optic neuropathy: a rare case report. International Journal of Research and Review. 2020; 7(2): 13-17.

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