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"Ethambutol Induced Optic Neuritis – A Case Series"

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ABSTRACT:
Ethambutol, a key component of anti-tubercular therapy, is associated with optic neuropathy, potentially leading to irreversible visual impairment. This case series reports three patients who developed ethambutol-induced optic neuritis (EON) after varying durations of therapy. All patients presented with progressive visual deterioration, defective colour vision, and optic disc changes on fundoscopic examination. Visual evoked potential (VEP) testing confirmed prolonged P100 latency in all cases, supporting the diagnosis of EON. Discontinuation of ethambutol was initiated promptly, and patients were managed with empirical corticosteroids, multivitamins, and zinc supplementation. While partial visual recovery was observed, residual deficits persisted, highlighting the unpredictable nature of EON. This case series underscores the need for routine ophthalmologic monitoring in patients receiving ethambutol, particularly those with risk factors for toxicity. Early detection and timely intervention remain crucial in mitigating long-term visual sequelae.

Introduction

Ethambutol is a primary chemotherapeutic agent commonly used in tuberculosis treatment during both the intensive and continuation phases.[1] It is administered alongside other anti-tubercular medications to help prevent drug resistance.[2] The most notable adverse effect of this bacteriostatic drug is optic neuritis.[3] Globally, approximately 9.2 million new tuberculosis cases are reported annually, with nearly 100,000 individuals developing toxic optic neuropathy as a consequence of ethambutol therapy.[4] Despite these figures, current estimates suggest that ethambutol-induced optic neuritis (EON) occurs in only 1–2% of patients receiving the drug.[5]

Early identification of EON is crucial, as delayed detection may result in permanent visual impairment. However, its clinical presentation can vary, making timely diagnosis challenging. This case series aims to highlight the diverse manifestations of EON, emphasizing the importance of ophthalmologic monitoring and early intervention in preventing irreversible vision loss. Three cases of EON were diagnosed at our Ophthalmology Outpatient Department (OPD) between July and October 2023 presented here to describe the clinical presentation of ethambutol-induced optic neuritis (EON) in patients undergoing anti-tubercular therapy, to highlight the variations in visual impairment, colour vision defects, and fundoscopic findings associated with EON and to emphasize the importance of routine ophthalmologic screening for early detection and prevention of irreversible vision loss in patients on ethambutol therapy

Scenario 1: Ethambutol-Induced Optic Neuropathy in a 48-Year-Old Female

A 48-year-old woman presented with a progressive decline in vision affecting both eyes, with more severe involvement in the left eye over the past two months. She had a prior diagnosis of genitourinary tuberculosis and had been receiving a fixed-dose combination (4FDC) anti-tubercular regimen for five months. She had no known comorbidities or concurrent medication use.

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On examination, her Best-Corrected Visual Acuity (BCVA) was recorded as 6/36 in the right eye, improving to 6/24p with pinhole correction, while in the left eye, it was 6/36p with no improvement on pinhole testing. Colour vision impairment was observed in both eyes. Anterior segment evaluation revealed a Grade 1 relative afferent pupillary defect (RAPD) bilaterally.

Fundoscopic assessment indicated clear media, hyperaemic optic discs with indistinct nasal and temporal margins, which were more pronounced in the left eye. Additionally, vessel tortuosity was noted, and the foveal reflex appeared dull in both eyes (Figure 1). Visual Evoked Potential (VEP) testing showed prolonged P100 latency in the right eye (Figure 2). Based on these clinical findings, a diagnosis of ethambutol-induced optic neuropathy was confirmed.

The patient was advised to discontinue ethambutol immediately and was initiated on empirical treatment with oral corticosteroids, multivitamins, and zinc supplementation. At follow-up, her vision remained at 6/36 in both eyes, with pinhole improvement to 6/24 in the right eye, though colour vision impairment persisted bilaterally.

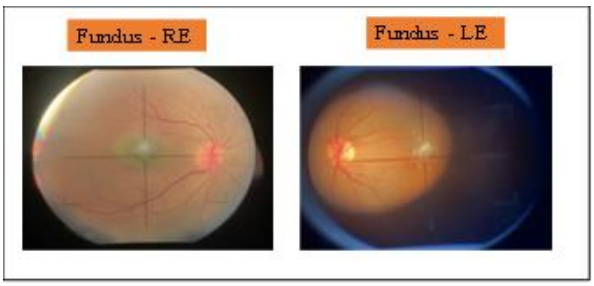

Figure 1 Fundus examination with blurred nasal and temporal margins (scenario 1)

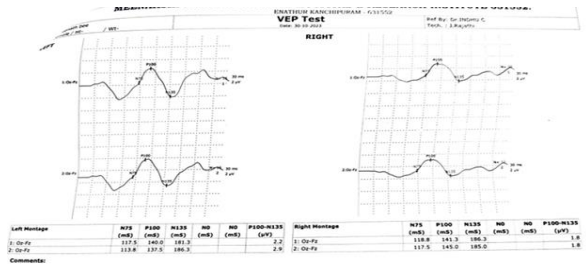

Figure 2 Visual Evoked Potential with prolonged P100 latency in right eye (scenario 1)

Scenario 2: Ethambutol-Induced Optic Neuropathy with Macular Oedema in a 47-Year-Old Female

A 47-year-old woman presented with progressively worsening vision in her right eye. She had been diagnosed with Pott's spine and had been undergoing 4FDC anti-tubercular therapy for four months. Her medical history was notable for diabetes mellitus and hypertension, both of which she had been managing with regular medication for the past decade.

Upon examination, her visual acuity was recorded as 2/60 in the right eye and 6/18p in the left eye, with no improvement on near vision testing. Colour vision was impaired bilaterally. Anterior segment assessment identified a Grade 1 RAPD in both eyes.

Fundoscopic evaluation revealed blurred nasal disc margins along with hard exudates at the macula. Optical Coherence Tomography (OCT) confirmed the presence of macular oedema (Figure 3). VEP testing indicated prolonged P100 latency, suggestive of an optic nerve conduction defect (Figure 4). Based on these findings, the patient was diagnosed with ethambutol-induced optic neuropathy with concurrent macular oedema.

Ethambutol was discontinued, and she was transitioned to an alternative anti-tubercular regimen that excluded ethambutol, replacing it with levofloxacin (10–15 mg/kg/day). Additionally, empirical treatment with systemic corticosteroids, multivitamins, and zinc supplements was initiated.

At follow-up, there was an improvement in visual acuity to 6/60 in the right eye, while the left eye remained stable at 6/18. However, bilateral colour vision deficits persisted.

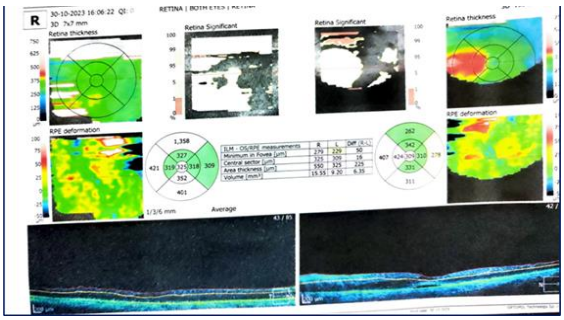

Figure 3 Optical Coherence Tomography (OCT) with macular oedema (scenario 2)

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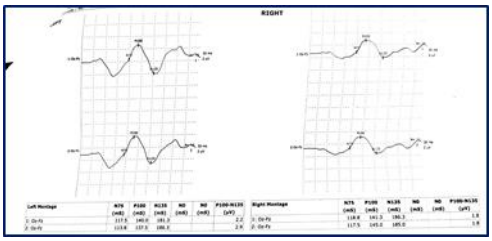

Figure 4 Visual Evoked Potential indicative of optic nerve conduction defect (scenario 2)

Scenario 3: Ethambutol-Induced Optic Neuropathy in a 45-Year-Old Female

A 45-year-old woman presented with a sudden decline in vision that had developed over three days. She had a history of tubercular ascites and was initially started on anti-tubercular therapy (ATT) in October 2022. However, the treatment was discontinued due to suspected drug-induced liver toxicity. Following a recurrence of tuberculosis, she was restarted on a 4FDC regimen for ten days.

On examination, her visual acuity was 3/60 in the right eye and 6/24p in the left eye, improving to 6/18 with pinhole correction. A Grade 1 RAPD was detected in both eyes. Fundoscopic evaluation revealed hyperaemic optic discs, and colour vision testing demonstrated difficulty in perceiving primary colours bilaterally. VEP testing showed prolonged P100 latency, indicative of impaired optic nerve conduction.

A diagnosis of ethambutol-induced optic neuropathy (EON) was made. The patient was advised to discontinue ethambutol and was transitioned to an ethambutol-free ATT regimen, replacing ethambutol with levofloxacin (10–15 mg/kg/day).

Discussion

Fixed-dose combination (FDC) therapy consists of a standardized formulation of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol. Under the National Tuberculosis Elimination Programme (NTEP), the current anti-tubercular treatment (ATT) regimen includes 275 mg of ethambutol during both the intensive and continuation phases. The incidence of ethambutol-induced ocular toxicity varies significantly across studies, with rates reported between 1% and 2% at a dosage of 15 mg/kg per day. This risk increases to approximately 5%–6% when the dosage is raised to 25 mg/kg/day and can reach up to 18% at doses of 35 mg/kg/day. Although toxicity most commonly develops between three to five months of therapy, it can manifest as early as one month or, in some cases, as late as a year after initiating treatment.[6]

Incidence and Risk Factors for Ethambutol-Induced Optic Neuropathy (EON)

The incidence of EON varies significantly across studies, influenced by factors such as dosage, duration of therapy, and patient-specific risk factors. The case series presented here aligns with the findings of Chaitanuwong et al., who identified older age (>60 years) and smoking as significant risk factors for EON, even though none of our cases were smokers or elderly.[7] Garg et al. reported a 12.6% incidence of colour vision abnormalities and a 9.4% incidence of visual acuity loss among tuberculosis patients receiving ethambutol under the RNTCP-DOTS regimen, suggesting that ocular toxicity is a relevant concern even in monitored treatment settings.[8] In our case series, all three patients developed visual impairment within five months of therapy initiation, reinforcing the notion that toxicity can occur despite standard dosage recommendations.

Clinical Presentation and Diagnostic Findings

Ethambutol toxicity typically manifests as bilateral, symmetrical, and painless loss of central vision, with colour vision deficits being one of the earliest indicators. In our case series, all three patients exhibited colour vision impairment, aligning with the findings of Dave et al., who noted reduced visual acuity and RNFL thinning in a subset of patients after two months of ethambutol therapy.[9] Additionally, Song et al. described a case of EON where vision recovered significantly after discontinuation, a pattern observed in our cases as well, though the extent of improvement varied.

When comparing the three cases in our series with existing literature, Case 1 presented with bilateral vision loss, more pronounced in the left eye, which aligns with the gradual onset reported by Sheng et al., who documented an asymmetric clinical manifestation of EON with initial unilateral involvement progressing to both eyes. Case 2, which involved macular oedema, is an

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unusual presentation compared to typical cases of ethambutol toxicity. However, studies like Sitaula et al. and Kandel et al. have reported subclinical toxicity with macular involvement seen in OCT imaging, suggesting that structural damage may precede significant functional loss. Case 3 had the most acute onset of symptoms, presenting within just two weeks of therapy, resembling the early-onset cases described by Shah et al., who highlighted rare but rapid manifestations of EON.

Sivakumaran et al. reported cases of EON with onset ranging from 2.5 to 12 months, emphasizing the unpredictable nature of toxicity onset.[10] Our cases developed symptoms within a window of two to five months, consistent with the expected time frame reported by Shah et al., who noted that optic neuropathy typically manifests within 4–12 months of therapy.[11] However, one of our patients experienced symptoms after just two weeks of treatment, mirroring rare early-onset cases such as the one reported by Shah et al.

Visual Recovery and Prognosis

Visual recovery following ethambutol discontinuation remains unpredictable, as demonstrated in studies by Kandel et al. and Srithawatpong et al.[12,13] Kandel et al. observed significant changes in ERG parameters, suggesting subclinical toxicity even when overt symptoms were absent..[12] Similarly, Srithawatpong et al. found that good initial visual acuity was a strong predictor of favourable recovery, a finding reflected in our cases, where patients with better baseline vision showed relatively improved outcomes.[13] Our Case 1 exhibited stable but incomplete recovery, supporting the findings of Song et al., where partial visual improvement was noted post-discontinuation.[14] Case 2, which involved macular oedema, showed the least recovery, highlighting the potential for irreversible damage when structural involvement is significant.

MacVinish et al. highlighted inconsistencies in visual monitoring protocols across different healthcare settings, reinforcing the importance of standardized screening guidelines.[15] The RNTCP's shift to a daily regimen with a prolonged duration of ethambutol use, may increase the risk of optic neuropathy, further underlining the necessity of early detection.[8]

Management Strategies and Implications for Clinical Practice

Early recognition and cessation of ethambutol remain the cornerstone of managing EON. Our case series supports the approach of transitioning to an ethambutol-sparing regimen, as advocated by Garg et al. and Sitaula et al., who emphasized the role of alternative treatment strategies in preventing irreversible vision loss.[8,16] While nutritional supplementation and corticosteroids were empirically used in our cases, there is currently no universally accepted treatment for ethambutol-induced optic neuropathy, as noted by Chaitanuwong et al. and Sethi et al.[7,17]

Role of screening

All newly diagnosed Tuberculosis patients should receive a baseline ophthalmological examination including visual acuity, colour vision, dilated fundus optic nerve examination and VEP before commencing ATT.[18] Frequency of examination is monthly for doses greater than 15mg/kg/day.[2] However lower doses may also warrant monthly review especially in patients with increased risk of toxicity like in associated chronic renal failure, diabetes, hypertensive, alcohol abuse, malnourishment, old age, low weight.[6]

Conclusion

Earlier studies showed that ocular toxicity caused by ethambutol as largely reversible, while with time it has been found that the reversibility remains variable. Partial recovery is achieved with increased emphasis on early detection and management, though it may be associated with variable loss of visual function. Therefore, all patients on ethambutol treatment need to be monitored for ocular toxicity remains a significant yet under-recognized complication of tuberculosis treatment. This case series highlights the variable presentation, diagnostic challenges, and unpredictable visual outcomes associated with EON. Given the increasing duration of ethambutol therapy in standardized regimens, routine ophthalmologic screening and early intervention are crucial to minimizing visual morbidity. Future research should focus on identifying reliable biomarkers for early detection and potential therapeutic interventions to mitigate vision loss in affected patients.

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