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**Vivekanand Undrakonda, Yashodhara B. M., Sarita Gonsalves,
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ABSTRACT

Introduction: Ethambutol related ocular toxicity, is a well-documented fact. In spite of this a regular visual acuity examination is missed during treatment and follow-ups.

Case Report: A 35-year-old male diagnosed with tuberculosis of spine, who was on antitubercular drugs for more than one year presented with complains of acute diminution of vision in both eyes two months following cessation of ethambutol. Visual electrode potential (VEP) showed prolongation of latency of P100 bilaterally based on which a diagnosis of ethambutol induced bilateral retrobulbar neuritis was made. Patient was started on intravenous methylprednisolone 1 g/day for three days which was followed by 11 days of oral steroids (1 mg/kg) which was tapered off over next 15 days. On follow-up patient showed signs of improvement in visual acuity and visual fields over the next six months.

Conclusion: Visual symptoms may revert if prompt action is taken that include discontinuation of ethambutol and supplementation of pyridoxine along with steroids like in our case. Pharmacovigilance on patients receiving antitubercular drugs for exact dosage, drug combinations and duration is necessary to avoid untoward complications.

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CASE REPORT

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Keywords: Antitubercular drugs, Ethambutol toxicity, Retrobulbar neuritis, Scotoma, Visual acuity

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INTRODUCTION

Acute onset of painless loss of vision in both eyes in a patient who is on antitubercular drugs pointing towards ethambutol toxicity, which is a well-documented fact. Ethambutol can affect the peripheral optic nerve fibers, causing defects in the peripheral visual field. Although optic neuritis is the most common side effect, retrobulbar neuritis is also a well-documented fact with involvement of either axial fibres or periaxial fibres [1, 2].

Dose related ethambutol related retrobulbar neuritis in patients who received it for more than two months was reported as 18% in patients receiving >35 mg/kg/day, 5–6% with 25 mg/kg/day and <1% with 15 mg/kg/day [3].

Rarely, it can cause visible retinal manifestations, including hyperemia and swelling of the optic disc, flame-shaped hemorrhages on the optic disc and in the retina, and macular edema. Other rarer side effects of ethambutol

include peripheral neuropathy, cutaneous reactions (rash, pruritus, urticaria, etc.), thrombocytopenia and hepatitis [4].

CASE REPORT

A 35-year-old male presented to our ophthalmology outpatient department with chief complaints of marked painless diminution of vision (left eye > right eye) over a period of three days. His best corrected visual acuity recorded was 6/36 in right eye and 1/60 in left eye (Snellen chart). Gross observations of the anterior segments of both eyes were normal except for ill-sustained pupillary response to light in both eyes. Dilated funduscopy was unremarkable.

One year back, he was diagnosed with tuberculosis of spine (thoracolumbar vertebra) based on a history of chronic cough, weight loss, backache, loss of appetite and results of diagnostic tests such as hemogram showed markedly elevated erythrocyte sedimentation rate (ESR) of 99 mm/hr, hematocrit of 36.2% with a bone scan with Tc-99m MDP which revealed multiple osteoblastic changes over T7 to T12 with multiple bilateral rib involvement. Following which a magnetic resonance imaging scan (plain and contrast) of lumbosacral spine showed features suggestive of diffusely infiltrating disease, with a possibility of multifocal tuberculosis in same region (Figure 1). Other parameters such as blood glucose, chest X-ray (Figure 2), liver function tests and renal function test were normal. Sputum test results were negative for acid-fast bacilli. The patient was started on antitubercular (ATT) drugs-isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1500 mg/day and ethambutol 1200 mg/day with vitamin B6 20 mg/day. Two months after initiation of ATT patient underwent a detailed ophthalmic examination which included visual acuity examination, macular function tests, and visual fields, all of which were unremarkable. After three months of initiation of ATT with four drugs, patient was advised to stop pyrazinamide and ethambutol and continue on two drugs isoniazid and rifampicin (which comes as combination tablet) as part of continuous phase treatment. The patient was lost to follow-up for next nine months. On repeat, consultation after one year patient was found to be still on isoniazid, rifampicin (combination tablet) and ethambutol, although he was advised to stop ethambutol three months after initiation of ATT. A repeat MRI scan of spine was performed after one year after initiation of ATT showed signs of improvement following which ethambutol was stopped and patient was advised to continue on isoniazid 300 mg/day, rifampicin 600 mg/day, and vitamin B6 20 mg/day for 6 more months. Four months following stopping of ethambutol patient presented with gross diminution of vision in both eyes.

Investigations

Visual field assessment using Goldman perimeter showed presence of gross central visual field (CVF) defects with Red-green dyschromatopsia. Visual electrode potential (VEP) showed prolongation of latency of P100 bilaterally. Computed tomography scan of brain and MRI scan of optic nerve both with and without contrast were normal (Figure 3). The cANCA was negative. A cerebrospinal fluid examination could not be performed.

Treatment

Based on the findings of VEP patient was started on intravenous methylprednisolone 1 g/day for three days which was followed by 11 days of oral steroids (1 mg/kg) which was tapered off over next 15 days.

Figure 1: Magnetic resonance imaging scan of spine showing diffuse multifocal tuberculosis of T7 to T12.

Figure 2: Normal chest X-ray.

Figure 3: Normal magnetic resonance imaging scan of optic nerve.

Outcome and follow up

After one month, during review patient showed signs of improvement in visual acuity and visual fields. His visual acuity improved to 6/24 in right eye and 3/60 in left eye. Visual field assessment showed constriction in central visual field defects in the subsequent follow-ups.

DISCUSSION

Antitubercular drugs produce unwanted side effects, especially when used at high dosages and usually for periods of more than two months [5, 6]. Retrobulbar neuritis, optic neuropathy and chiasmopathy due to ethambutol is a known neurotoxic complication. The onset of visual symptoms can occur within a period of 10 days to 90 days after initiation of therapy [7–9]. Detailed ophthalmoscopic examination reveals a bilateral and often an unequal decrease in visual acuity, loss of color vision, bitemporal hemianopsia or centrocecal scotoma on perimetry. Fundoscopy generally shows bilateral disc hyperemia with blurred borders. Rarely, fundoscopy may be normal like in our case report. Methylprednisolone along with cessation of the drug is considered useful, as was seen by the visual improvement in our patient. However, the recovery is often incomplete.

Visual acuity, contrast sensitivity, and multifocal ERG are sensitive tests to detect ethambutol toxicity in subclinical stages and hence very useful tools for monitoring patients under ethambutol therapy for ocular toxicity [10]. MRI scans of the optic nerves and chiasm, with normal findings in toxic and/or nutritional optic neuropathy, could be useful to differentiate between bilateral centrocecal scotomas and compressive or infiltrative lesions of the optic chiasm.

After three months of initiation of ATT with four drugs, our patient was instructed to stop pyrazinamide and ethambutol and continue on two drugs isoniazid and rifampicin which comes as combination tablet as part of continuous phase treatment for one year. But unfortunately, patient misunderstood the instructions as two tablets continued isoniazid, rifampicin which comes as a combination tablet with another tablet ethambutol for next nine months and was never on follow-up during this period.

After one year when our patient came for follow-up, he was instructed to stop ethambutol. Four months following discontinuation of ethambutol, which remains the mainstay of treating ethambutol-associated ocular toxicity, our patient developed bilateral retrobulbar neuritis.

Isoniazid associated combination formulations are easier to administer and also may reduce medication errors. These formulations are means of minimizing inadvertent monotherapy. It is quite common for patients with tuberculosis to be taking a variety of other medications, hence combination therapy is preferred to monotherapy to improve compliance in patients with

comorbid conditions. The combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for two months followed by combination of rifampicin and isoniazid for a total period of 6, 9, 12 or 18 months is the most frequent protocol used for treatment of spinal tuberculosis [11].

Early detection of adverse effects of drugs, failure of treatment and emergence of drug resistance due to non-compliance could be overcome by establishing a human bond between the patient and the provider through DOTS. In the developing world, evidence from uncontrolled studies shows that the introduction of DOTS has increased completion of therapy and cure rates from 25–50% (with unsupervised treatment) to 80–90%, with relapse rates of less than 5% [12, 13]. Despite all the advantages of DOTS regimen, many orthopedic surgeons continue to give daily regimens. This is basically due to the fact that the efficacy of short-course intermittent therapy like DOTS regimen is not scientifically proven [14].

How could such complications be prevented: The first step is to identify patients in whom ethambutol is relatively contraindicated. These include patients who are unlikely to notice or describe visual symptoms, such as patients with dementia, mental retardation and children. Others include patients with pre-existing ophthalmological diseases with poor baseline vision. These patients should not be treated with ethambutol. The second step is to educate all patients treated with ethambutol on its side effects. Third step: Patients taking ethambutol should be instructed to discontinue the drug immediately at the onset of any visual symptoms and seek medical consult. Fourth step: When patients are prescribed combination therapy they should be closely monitored for compliance as well as side effects. The duration therapy for each drug should be defined and monitored. Physicians prescribing the drug should be aware of this and the drug should be used with proper patient education and ophthalmological monitoring especially when used in combination [15–19].

An immunological reason for bilateral retrobulbar neuritis was suspected and cANCA was performed to rule out other collagen vascular disorders and granulomatous conditions. Although few positive c-ANCA test results have been reported in patients with tuberculosis, Hodgkin's lymphoma, human immunodeficiency virus infection, nasal septal perforation, monoclonal gammopathies, and drug-induced Wegener-like disease. In this case, cANCA was negative [20–21]. Although the MRI scan showed no involvement of optic nerve, in view of positive VEP findings patient was started on methylprednisolone and oral steroids [22].

CONCLUSION

It is necessary that practitioners watch patients receiving antitubercular carefully for exact dosage, drug combinations and duration in order to avoid untoward complications. Visual symptoms may revert if prompt

action is taken that include discontinuation of ethambutol and supplementation of pyridoxine along with steroids like in our case. It is also vital that such cases are reported through active pharmacovigilance programs, so that we can prevent future errors.

Author Contributions

Vivekanand Undrakonda – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Yashodhara B. M. – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Sarita Gonsalves – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Shashikiran U. – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Smita Kapoor – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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