

## OCULAR COMPLICATIONS OF ANTI TUBERCULAR DRUGS

Dr. Manpreet Bhalla MD<sup>1\*</sup>, Dr. Shayana Bhumbra<sup>2</sup>, Dr. J. S. Bhalla<sup>3</sup><sup>1</sup>HOD (Microbiology), (NITRD) National Institute of TB & Respiratory Diseases, N. Delhi.<sup>2,3</sup>DDU Hospital, Hari Nagar, N. Delhi.**\*Corresponding Author: Dr. Manpreet Bhalla MD**

HOD (Microbiology), (NITRD) National Institute of TB &amp; Respiratory Diseases, N. Delhi.

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**ABSTRACT**

Infecting millions of people worldwide, TB is still the commonest infectious disease and a major public health problem. Frequently used Anti tubercular drugs including Ethambutol, INH, Streptomycin, & even newer ones like Linezolid are associated with Ocular adverse reactions. It is extremely important for treating physicians to be aware of these potentially sight threatening side effects, so that safe dosage is prescribed & drug should be stopped or withdrawn before irreversible damage occurs. Besides sensitising them, educating the patients for early detection of the ocular manifestations is extremely important so that proper Ophthalmic evaluation of affected patients at follow-up visits is undertaken.

**KEYWORDS:** Optic Neuropathy, Retrobulbar neuritis, Ethambutol induced Optic neuropathy, Dyschromatopsia, Centrocecal scotoma.

**INTRODUCTION**

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* complex, has been prevalent in our country for years and still remains a major health concern. India accounts for about a quarter of the global TB burden. Despite there being a cure for TB, it still remains one of the leading causes of mortality worldwide. As per the WHO Global Tuberculosis Report 2017, the total notified cases of TB in India in 2016 were 1 936 158.<sup>[1]</sup> Apart from these, there are a lot of “missing” cases every year that are either not notified, remain undiagnosed or are treated in the private sector. The Government of India, under RNTCP (Revised national tuberculosis control programme) is providing quality health care to those suffering from this disease by providing antitubercular drugs at the various DOTS (Directly observed treatment short course) centres. However, it is important to impart information to the patient regarding the common drug related adverse effects and their preventive strategies. Owing to its extensive vascularity, the eye is particularly vulnerable to side effects of systemically administered drugs which may selectively accumulate in different tissues. It is imperative to detect the side effects arising out of such accumulation well in time to prevent development of permanent complications which may otherwise be avoidable.

An interplay of various factors leads to development of ocular side effects of systemic medications. These factors may be patient related, or drug related. Patient related factors include patient age, co-existing diseases,

renal or hepatic disease which may alter drug metabolism. Genetic factors may also play a role which may not be consistently observed in all patients.<sup>[2]</sup> Drug related factors include duration of treatment, interactions with concurrent medication, half-life and tissue deposition of the drug under question. Environmental factors may also contribute and these usually result in erratic reactions. Simultaneously, certain drugs may cause idiosyncrasy where unpredictability is the rule.<sup>[3]</sup> It is also important to determine whether the ocular complaint is arising out of initiation of a new systemic drug, or due to improper or altered dosage. There is paucity of literature describing ocular side effects exclusively due to all anti tubercular drugs, and this review intends to do the same to devise a preventive strategy.

**Ethambutol**

Ethambutol hydrochloride, one of the first line medications to treat TB, has been known to cause optic neuropathy.<sup>[4]</sup> The incidence of EON (ethambutol induced optic neuritis) is approximately 1%.<sup>[5-8]</sup> Retrobulbar neuritis is the most common, with involvement of either axial fibres- causing decreased visual acuity, colour vision abnormalities and central scotoma or, less commonly, periaxial fibres – causing peripheral visual field defects, but the colour vision and visual acuity remains unaffected in this type. A mixed pattern is also possible.<sup>[9,10]</sup> Exact mechanism of action of its toxicity is still unclear. Evidence from Animal studies have revealed ethambutol toxicity in the retinal ganglion neurons of rodents. The zinc chelating

properties of ethambutol & its metabolite have been hypothesized to contribute to its noxious effects. It causes a calcium flux into the mitochondria and excitotoxicity.<sup>[11,12]</sup> Downstream effector caspase-3 and caspase-6 are postulated biochemical pathways that cause neuropathy.<sup>[13]</sup>

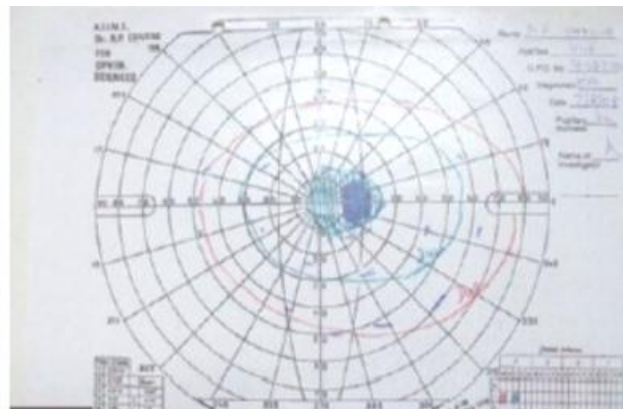
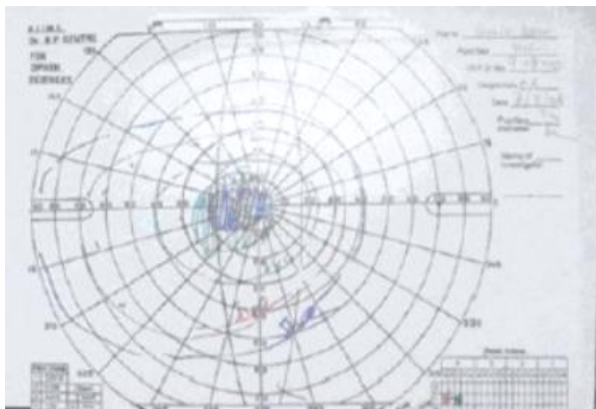
Ocular toxicity due to ethambutol (1%–5%), is described as dose and duration dependent & is also reversible.<sup>[9]</sup> Risk of EON is higher at dosages of 25 mg/kg/day or more. Should this occur, the dosage should be reduced to 15 mg/kg/day or less, which is considered both relatively safe and efficacious.<sup>[14]</sup> Prompt recognition of this association is critical in preventing irreversible, profound visual loss. As the major excretion pathway of ethambutol is via the kidneys, patients with poor renal function are at higher risk of ocular toxicities. Other factors that predispose subjects to toxicity include diabetes and optic neuritis related to tobacco and alcohol consumption, elderly.<sup>[15-17]</sup> Visual symptoms appear between 4-12 months of treatment.<sup>[9,18-21]</sup>

More recently, the Revised National Tuberculosis Control Program (RNTCP) in India has suggested an extension of duration for ethambutol for up to six months

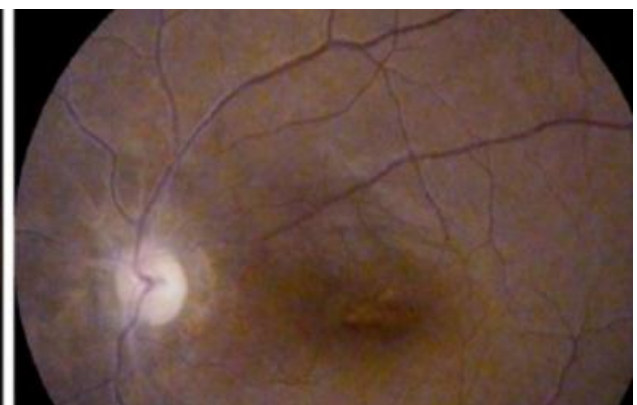
for new cases (2HRZE + 4HRE) and for 24-27 months in cases of MDR (multi-drug resistant tuberculosis). Additionally, there is an increasing trend for physicians to use higher doses of ethambutol (up to 1200 mg/day), especially in drug-resistant tuberculosis. An increase in both these variables is likely to significantly increase the risk of ocular complications.

EON, although is classically described as reversible; there are multiple case reports.<sup>[16-19, 21,22]</sup> of patients with permanent visual impairment despite cessation of the drug, hence, questioning its “reversibility”. However, queries were raised again since isoniazid was not stopped in these patients and that could also be a possible cause.

Clinically, patient may present with bilateral symmetric painless diminished vision, colour vision defects (mainly red green), central scotomas (fig1-2), peripheral field defects.<sup>[23]</sup> Fundus may show bilateral disc pallor (fig3-4). In view of vision threatening side effects of ethambutol It is recommended to record visual acuity, field charting, colour vision, contrast sensitivity, fundus examination of a patient before initiating ethambutol.



**Fig: 1, 2.** Goldman visual fields of the same patient showing bilateral centrocecal scotomas. *Sharma P, Sharma R. Toxic optic neuropathy. Indian J Ophthalmol, 2011; 59: 137-41.*



**Fig: 3, 4.** Fundus photo showing bilateral disc pallor in a patient with ethambutol toxicity. *Sharma P, Sharma R. Toxic optic neuropathy. Indian J Ophthalmol, 2011; 59: 137-41.*

**Isoniazid**

Yet another quintessential first line drug, isoniazid, is believed to be a causal agent for retrobulbar neuritis. The risk increases in patients with renal dysfunction & malnutrition. Visual symptoms usually occur within 10 days of initiation of the drug, but may occur after 2-3 months as well.<sup>[24-26]</sup> funduscopy reveals bilateral disc edema. The mechanism is postulated to be due to INH induced loss of pyridoxine in the urine or isoniazid blockade of pyridoxal phosphate synthesis which depletes neurotransmitters.<sup>[25]</sup> Immediate cessation of the drug, administration of pyridoxine 25-100mg/day may reverse the neuropathy.<sup>[23,27]</sup> the use of methylprednisolone is also considered useful.

As per the Tuberculosis and Chest Service of the Department of Health of Hong Kong Special Administrative Region, If a patient on ATT develops optic neuritis, ethambutol is stopped and if no visual improvement occurs in 6 weeks, isoniazid is also stopped.<sup>[28]</sup>

**Streptomycin**

Streptomycin, a first line ATT given i. m, causes pseudotumor cerebri. The drug is to be avoided in kidney dysfunction and myasthenia gravis patients. All toxic effects are reversible on discontinuing the drug. Kanamycin and Amikacin are also known to produce effects similar to streptomycin.<sup>[29]</sup>

There are reports of optic neuritis developing during streptomycin therapy, which improved on discontinuing the drug.<sup>[30-33]</sup>

**Thiacetazone**

can produce severe cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva.

**Rifampicin**

It can produce conjunctivitis and orange staining of contact lenses. These discolorations may be bothersome to the patient but do not require medical attention.<sup>[34,35]</sup>

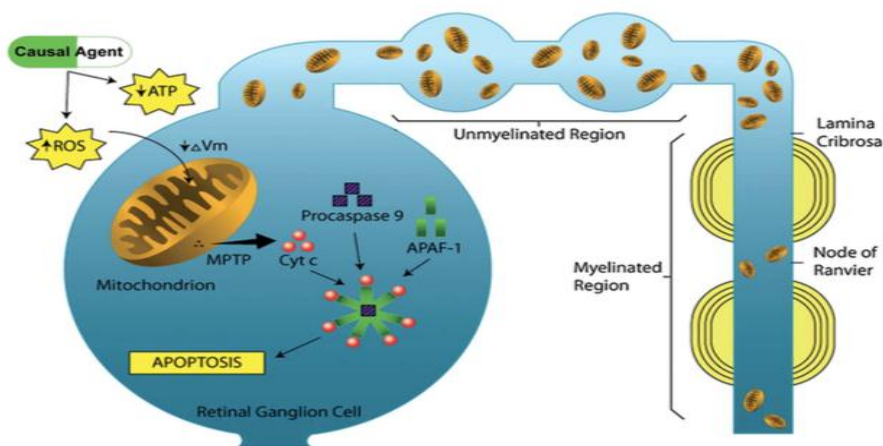
**Linezolid**

In the most recent treatment guidelines by the World Health Organization (WHO, 2016) linezolid is recommended as a core second-line drug in the MDR-TB regimen.<sup>[36]</sup> LINEZOLID an oxazolidinone antibiotic, for treating MDR,XDR-TB, also causes duration dependent optic neuropathy (mean of 9 months)<sup>[37,38]</sup> and peripheral neuropathy. Although 2 cases have been reported after a short duration also.<sup>[39,40]</sup> the average duration is of 28 days.<sup>[41]</sup> Linezolid causes diminution of vision, defective color vision, central & superior field defects.<sup>[42]</sup> Earlier studies reported lower prevalence of optic neuropathy among patients on linezolid ranging between 1.3% and 3.3%.<sup>[43-45]</sup> However, two recent studies reported prevalence of 13.2% and 8%.<sup>[46,47]</sup> The mechanism of action of linezolid's toxicity is believed to be Mitochondrial dysfunction. Low folate causes the plasma homocysteine to increase, which may inhibit neuronal mitochondrial function.<sup>[48]</sup> Linezolid inhibits protein synthesis by preventing formation of the ribosome complex that initiates protein synthesis. Its unique binding site located on 23S ribosomal RNA of the 50s subunit results in no cross resistance with other drug classes. Long-term linezolid interferes with bacterial ribosomes and also with mammalian ribosomes, thereby disrupting mitochondrial oxidative phosphorylation and protein synthesis.<sup>[49]</sup>

Mitochondria, through their respiratory chain, are the major source of cellular reactive oxygen species (ROS) as a byproduct of ATP synthesis. The disruption of oxidative phosphorylation at any step in the respiratory chain leads to considerable energy depletion coupled with the accumulation of ROS in the Retinal Ganglion Cells.



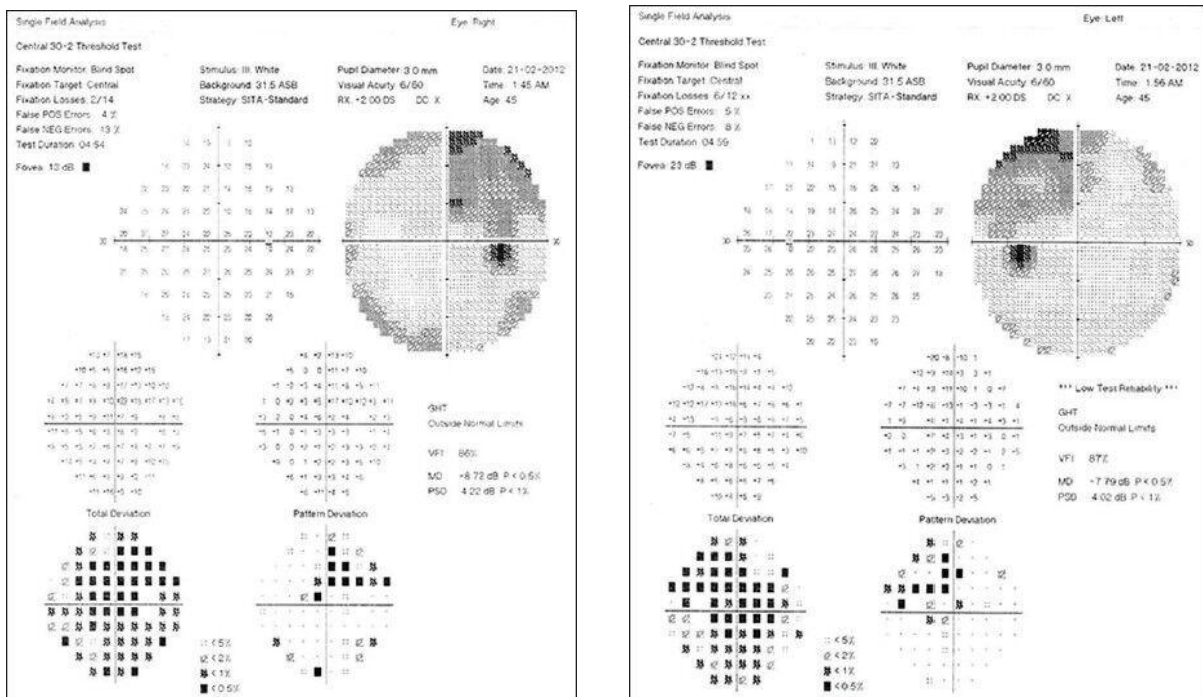
This accumulation of ROS lowers the electrical potential across the mitochondrial membrane and this opens the mitochondrial permeability transition pores, which acts as an apoptotic switch by releasing factors promoting cell death such as cytochrome c.



**Fig. 5. Pathophysiology of mechanism of action of linezolid.**



**Fig: 6, 7. Fundus photos showing disc edema OU in a patient on linezolid Divya Karuppannasamy, Andavar Raghuram, Devisundaram Sundar. Linezolid-induced optic neuropathy. Indian J Ophthalmol, 2014; 62(4): 497–500. doi: 10.4103/0301-4738.118451.**



**Fig: 8, 9. Visual field of both eyes showing quadrantanopia. Divya Karuppannasamy, Andavar Raghuram, Devisundaram Sundar. Linezolid-induced optic neuropathy. Indian J Ophthalmol, 2014; 62(4): 497–500. doi: 10.4103/0301-4738.118451.**

**Thiacetazone**

Thiacetazone can produce severe cutaneous reactions including Steven Johnson Syndrome affecting the skin and mucosa including conjunctiva. HIV positive patients are at increased risk for cutaneous reactions. Severe dry eye owing to extensive scarring of the conjunctiva may be a sequelae.<sup>[29]</sup>

**Ciprofloxacin**

One of the second line drugs – fluoroquinolones – rarely cause ocular toxicity. Diminished vision, changes in colour perception & eye pain occurred in <1% of cases.

Cases of reversible optic neuropathy due to ciprofloxacin have been reported. The mechanism of ciprofloxacin induced optic neuropathy remains unknown.<sup>[50,51]</sup>

**Common Clinical features of Toxic optic neuropathy**

Symptoms – Diminution of vision:-bilaterally symmetrical, painless, gradually progressive, dyschromatopsia.

Signs-

- Pupils-sluggish, no RAPD
- Optic disc- normal, swollen or hyperemic in early stages, temporal pallor later
- Visual field defect –centrocecal scotoma

**Prevention and management**

Increased suspicion and assessment of visual acuity and colour vision by the treating physician on every visit can help in early diagnosis and immediate referral to ophthalmologist. All the possible side effects and warning signs should be explained to the patient prior to starting therapy. Apart from Visual acuity and Colour

vision; Careful and thorough history, Pupillary reaction, Contrast sensitivity, Perimetry, Fundoscopy, Amsler grid test, Electrophysiological tests like VEP, ERG & RNFL thickness by OCT should be done and documented.

### Recommendations

It is imperative to formulate guidelines to do routine ophthalmic checkup in patients receiving Anti Tubercular treatment. Also, mandatory instructions need to be given to the patients about blurring of vision, noticing any nonseeing areas in the central field and difficulty in appreciating different colors. In addition to asking vision related questions during follow up of patients on ATT, Vision screening charts should be provided in all TB treating centres. If a patient on ATT develops optic neuritis –first stop ethambutol. If no visual improvement occurs in 6weeks, stop isoniazid also. Remember, if patient is on Linezolid – it could also be the cause of Optic neuritis.

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