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Anti tubercular treatment (ATT) induced optic nerve changes: An observational study

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Abstract: *Tuberculosis is the most common cause of infectious disease-related mortality worldwide. Ethambutol and isoniazid (INH) are synthetic first-line agents of the anti-tubercular treatment (ATT) against Mycobacterium tuberculosis. Ethambutol optic neuropathy is a well-recognized adverse ocular event in patients who receive the drug for the treatment of mycobacterial infections. However, most cases in literature are reversible. Optic nerve involvement is a rare side-effect of INH. Visual loss due to optic neuropathy is a rare side-effect of ATT particularly ethambutol and INH. The main aim of this study was to evaluate the ocular effect of ATT with Standard regimen and visual outcome. A total of 73 Patients who were diagnosed as a case of TB and on ATT, were included in this observational study conducted in the Department of Ophthalmology and TBCD, MLBMC, Jhansi. An assessment of present complains detailed clinical history (present and past). Ophthalmological check up as external examination of the eyes, visual acuity, torch light examination, slit lamp examination, colour vision, refraction, direct ophthalmoscopy, Gonioscopy, Perimetry, Fundus photography and OCT were done. MRI was done in special cases. Standard ATT regime HRZE (H: 8-10 mg/kg body weight, R: 8-10 mg/kg body weight, Z: 30–40 mg/kg body weight, E: 25-35 mg/kg body weight) was followed in this study with minimum 6 months of duration. The the male to female ratio was 1.52:1 and incidence of optic neuropathy was 9.59%. Most of them had pulmonary tuberculosis (87.67%).. Nutritional and toxic (toxic neuropathy caused by tobacco, alcohol and other drugs) optic neuropathy was main confounding factor.*

Keywords: *Anti-tubercular treatment (ATT), Fundus photography, Gonioscopy, OCT, optic neuropathy, Mycobacterium tuberculosis, Parimetry*

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I. Introduction

The optic nerve contains axons of nerve cells that emerge from the retina, leave the eye at the optic disc, and go to the visual cortex where input from the eye is processed into vision. There are 1.2 million optic nerve fibers that derive from the retinal ganglion cells of the inner retina.[1]. Optic neuropathies are disorders of the optic nerve involving degeneration of the nerve.[2] *Optic neuropathy* should not be confused with *optic neuritis*. Both can lead to vision problems; optic neuritis involves inflammation of the optic nerve while optic neuropathy refers to damage from any cause. Optic neuritis is one of the many causes of optic neuropathy. Optic neuropathies can be either hereditary or acquired. Acquired etiologies of optic neuropathy include ischemic, nutritional, and toxic types.[2,3] Drug-induced optic neuropathy is of the toxic type. Mechanisms of drug-induced optic neuropathy include mitochondrial dysfunction, disruption of blood flow to the optic nerve, and unknown mechanisms.[2] Common symptoms of optic neuropathy include decreased vision in the central field, which is typically bilateral but may be unilateral in some cases; visual-field defects; and swelling of the optic nerve.[4] The onset is typically slow and painless.[2] In drug-induced optic neuropathy, withdrawal of the offending drug can lead to relief of symptoms.[4,5] Since many of the medications known to cause optic neuropathy are common ones, it is important for pharmacists to be aware of this adverse effect in order to refer patients with these symptoms in a timely manner and avoid further, permanent damage.

Tuberculosis (**TB**) is an infectious disease usually caused by the bacterium *Mycobacterium tuberculosis* (MTB).[6] Tuberculosis generally affects the lungs, but can also affect other parts of the body.[1] Most infections do not have symptoms, in which case it is known as latent tuberculosis.[6] About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected.[6] The classic symptoms of active TB are a chronic cough with blood-containing sputum, fever, night sweats, and weight loss.[6] The historical term "**consumption**" came about due to the weight loss.[7] Infection of other organs can cause a wide range of symptoms.[8] Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze.[6][9] People with latent TB do not spread the

disease.[6] Active infection occurs more often in people with HIV/AIDS and in those who smoke.[6] Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids.[10]Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests.[10] For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued. [11]

Ethambutol: This drug, a first-line agent in the treatment and prevention of tuberculosis, causes numerous ocular adverse effects. It has been well documented to cause optic neuropathy in up to 5% of patients taking the drug.[3] The mechanism of this adverse effect is not completely clear, but has been speculated to be related to chelation of copper in retinal cells.[5] Most patients with this adverse effect had taken doses of 60 to 100 mg/kg/day with onset of symptoms after 2 to 12 months of treatment.[5,12]. Ethambutol-induced optic neuropathy is thought to be dose related; it occurs at rates of 18% of patients at a dose of 35 mg/kg/day, 5% to 6% at 25 mg/kg/day, and less than 1% at 15 mg/kg/day.[13] The vision loss associated with ethambutol has been commonly reported to be reversible; however, it may be irreversible in certain populations, including geriatric patients and those who received the drug chronically.[13] Ethambutol is contraindicated in patients with a history of optic neuritis unless clinical judgment warrants its use.[14] Baseline and periodic eye examinations should be conducted; the prescribing information for ethambutol recommends monthly examinations for patients taking >15 mg/kg/day.[14]

Isoniazid: This antibiotic is another drug used in the treatment and prevention of tuberculosis. It has been reported to cause optic neuropathy; however, since isoniazid is used in conjunction with ethambutol, which is also implicated in optic neuropathy, determining the cause of vision problems is often difficult.[15] Isoniazid-induced optic neuropathy is thought to be less frequent and reversible.[3]

II. Method and Material

A total of 73 Patients who were diagnosed as a case of TB and on ATT, were included in this observational study conducted in the Department of Ophthalmology and TBCD, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India over a period of 18 months from Feb. 2016 to July 2017. The procedures followed were in accordance with the ethical standards committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000. The necessary permission from the Ethical and Research Committee was obtained for the study.

Inclusion criteria:

1. Patients who had TB and on ATT with minimum 6 months of duration
2. Patients with HRZE standard ATT regime were included in the study.
3. Both male and female patients were included in the study.
4. There was no age limit in the study.

Exclusion criteria:

1. Patients with any Posterior segment surgery were excluded from the study.
2. Patients with primary, glaucomatous, and traumatic optic atrophy were excluded from the study.
3. Patients, who had previous history of taken medication which can causes optic neuropathy like phosphodiesterase type 5 (PDE-5) inhibitors, amiodarone, linezolid, were excluded from the study.

An assessment of present complains, detailed clinical history (present and past), and detailed history of taken ATT (Dose, regime, duration, continuation) dietary habit, any other medication and any ocular surgery/trauma. Age, sex, occupation, socio-economic status, personal history and BMI were recorded. Ophthalmological check up as external examination of the eyes, visual acuity, torch light examination, slit lamp examination, colour vision, refraction, direct ophthalmoscopy, Gonioscopy, Parimetry, Fundus photography and OCT were done. MRI was done in special cases.

Patients were diagnosed to have ocular toxicity if they had fundus changes like temporal or total disc pallor; colour vision abnormalities not attributable to any other cause or field changes like paracentral scotoma or peripheral visual field constriction which could not be explained by other causes

III. Results

Standard ATT regime HRZE (H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol) followed
H: 8-10 mg/kg body weight, R: 8-10 mg/kg body weight, Z: 30–40 mg/kg body weight, E: 25-35 mg/kg body weight.

Table -1: Age wise distribution of patients (n=73)

	Male	Female
No. of Patients included in study	44	29
Percentage (%)	60.27%	39.73%

Table -2: Type of TB in study patients (n=73)

Type of TB	No. of patients	Percentage (%)
Pulmonary TB	64	09
Extra-pulmonary TB	87.67%	12.33%

Table -3: ATT regimen induced ocular toxicity in study patients (n=73)

	Male	Female		Total	
No. of patients had fundus changes or field defect, or defected colour vision	04	03		07	
	All had pulmonary TB	Pulmonary TB- 02 (2.74%)	Extra-pulmonary TB-01 (1.37%)	Pulmonary TB- 06	Extra-pulmonary TB-01 (1.37 %)
Percentage (%)	5.48%	4.12%		9.59%	

IV. Discussion

Standard ATT regime HRZE (H: 8-10 mg/kg body weight, R: 8-10 mg/kg body weight, Z: 30–40 mg/kg body weight, E: 25-35 mg/kg body weight) was followed in this study with minimum 6 months of duration. The results of this study show that the male to female ratio in patients of tuberculosis was 1.52:1, which is in concurrence with other reports [19,20]. Most of them had pulmonary tuberculosis (87.67%). One female with ATT induced ocular toxicity had Tuberculous lymphadenitis. The incidence of ethambutol toxicity has been reported as varying from 0.5-4.3%(2% in some studies[16], in some others as 1.1-4.3%[17] and in yet another as 0.5-1.5%[18]) while in our study the incidence of ATT induced toxicity was 9.59 % . 04 male (5.48%) and 03 female (4.12%) with ATT had Optic nerve changes. In this study the nutritional and toxic (toxic neuropathy caused by tobacco alcohol and other drugs) optic neuropathy was main confounding factor which can alter the study results.

V. Conclusion

Many medications can cause ocular adverse effects, and the potential risks should be discussed with patients prior to initiating therapy. Prompt ophthalmic evaluation is paramount, and that, along with discontinuation of the offending drug when possible, constitutes the basis of treatment of drug-induced optic neuropathy.[5] While discontinuation of the drug is often recommended, this may not always be possible, as medications like amiodarone, linezolid, and ethambutol may be necessary to treat the patient optimally. In these circumstances, careful monitoring and ongoing care by an ophthalmologist is necessary. It may not be possible to know all drug-induced ocular adverse effects, but it is important to recognize that many systemic medications can affect eye health. Early detection can potentially prevent or minimize serious harm. Doctors should be aware that most patients experiencing drug-induced optic neuropathy will present with decreased vision. Any patient complaining of a sudden and painless decline in vision should be advised to report these changes immediately. All patients on ATT should undergo regular ophthalmological evaluation before and during the course of treatment.

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