Original Research Article

A Hospital Based Prospective Study to Assess the Ocular Manifestations of Anti-Tubercular Drugs in Patients Receiving Anti- Tuberculosis Treatment

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Abstract

Background: TB is still the most common infectious disease and a major public health problem, infecting millions of people worldwide. Among ATT, ethambutol is the most commonly implicated drug causing optic neuropathy. The aim of this study to assess the ocular manifestation of anti-tubercular drugs in patients receiving anti-tuberculosis treatment. **Material &Methods:** This study is an observational follow up study done on 80 patients of newly diagnosed drug susceptible pulmonary tuberculosis, referred to ophthalmology OPD in a Government Medical college, Sikar, Rajasthan were examined. All patients of newly diagnosed pulmonary TB on standard HRZE regimen were examined thoroughly before initiating ATT and thereafter every month up to 6 months during a period of one year. Socio demographic data with patient's personal identification information was recorded. All the patients were evaluated for best corrected visual acuity by illuminated Snellen chart for 20 feet distance. Colour vision was assessed using Ishihara chart. Visual field testing was done using the Carl Zeiss Meditec HFA 2 Humphrey field analyzer with 30-2 threshold programme, with dim ambient light source with full refractive correction. **Results:** Mean age of the patients is 32.56 year with maximum number of patients being in age group 18-30 years (56.25%). There were 45 (56.25%) males and 35 (43.75%) females. Colour vision was assessed using Ishihara colour vision plates. During study, it was observed that out of 160 eyes, 10 eyes of five patients (6.25%) showed colour vision abnormality at the end of 6 month follow up. All the patients were followed up at monthly interval up to 6 months and their visual acuity was tested, during which we found that decline in visual acuity from baseline was seen in 12 eyes of six patients (7.5%) in which 2 eyes of one patient had drop in visual acuity at 4th month follow up, 8 eyes of four patients had drop in visual acuity at 5th month follow up and 8 eyes of four patient at 6th month follow up. The most common defect seen was cecocentral scotoma in four (2.5%) eyes out of 160 eyes. Other defects seen were peripheral constriction (2.5%) and peripheral defect in different quadrant (1.25%). **Conclusion:** We found that ocular toxicity was seen in a significant number of patients (6.25%). The ocular toxicity of ethambutol in our patients had manifested in the form of changes in visual acuity, colour vision, visual field and fundoscopy picture.

Keywords: Visual Acuity, ATT, Tuberculosis, Ocular Manifestations, Colour Vision, Visual Field.

Introduction

Tuberculosis (TB) has been present since 460 BC, as the most widespread disease of the time, and it was fatal. TB is still the most common infectious disease and a major public health problem, infecting millions of people worldwide. India accounts for about a quarter of the global TB burden[1].

Single drug therapy can lead to the development of a bacterial population resistant to that drug. Inadequate treatment can lead to treatment failure, relapse, and drug resistance. Responsibility for successful treatment is assigned to the health care providers. First line antituberculosis drugs recommended by WHO are a combination of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions. The adverse drug reactions may be mild to severe[2,3]. Studies have shown that multidrug regimens can cause undesirable adverse drug reactions such as arthralgia, neurological disorders, gastrointestinal disorders, hepatotoxicity, and allergic reactions[4,5].

Carr and Henkindin 1962 first described the ocular side effect of Ethambutol[6]. Ethambutol is generally well tolerated, but it is known to cause optic neuritis, more specifically retrobulbar neuritis[7]. Ethambutol causes two types of optic neuritis: one is axial neuritis (central) and the other one is paraxial neuritis (peripheral). The central fibers of the optic nerve are most commonly affected, causing blurred vision, decreased visual acuity, central scotomas, and often loss of the ability to detect red and green. The peripheral fibers of the optic nerve are less commonly involved, so that visual acuity and colour vision may not be affected, but peripheral constriction of the visual fields occurs[8]. The exact pathophysiology of ethambutol optic neuropathy has not yet been identified. Mitochondrial disturbance, the zinc-chelating effect and its metabolite are the possible underlying mechanisms[6]. EMB toxicity is related to the dose and duration of treatment and in most of the cases it is reversible, but may occasionally become irreversible resulting in permanent visual impairment especially in the older population. Ithas been said that there is no so-called "safe-dosage" for EMB[10]. Isoniazid can rarely

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cause retro bulbar neuritis[7]. Rifampicin can produce orange colour tears and orange staining of contact lenses[11]. There are a number of uncertain and difficult areas in the recommendation of preventive measures against drug-induced ocular toxicity during anti-TB treatment. The management of EMB induced optic neuropathy involves immediate discontinuation of the drug[7]. If the optic neuritis fails to improve within 6 weeks after stopping EMB, INH should also be stopped. Pyridoxine 25-100 mg/day may be considered in isoniazid induced toxic neuropathy, particularly for those with risk factors like malnutrition, alcoholics[10]. The aim of this study to assess the ocular manifestation of anti-tubercular drugs in patients receiving anti-tuberculosis treatment.

Materials & methods

This study is an observational follow up study done on 80 patients of newly diagnosed drug susceptible pulmonary tuberculosis, referred to ophthalmology OPD in a Government Medical college, Sikar, Rajasthan were examined.

Inclusion criteria

1. Adult patients (above 18 years of age).
2. New cases of drug susceptible pulmonary TB receiving standard HRZE treatment regimen under DOTs therapy.

Exclusion Criteria

1. Patients having any major systemic illness (Diabetes mellitus, Hypertension, renal disease, demyelinating disease).
2. Patients having preexisting posterior segment pathology.
3. Patients having mature cataract or dense ocular media opacity.
4. Patients with preexisting colour vision defects.
5. All MDR-TB and XDR-TB category patients and who has received anti TB drugs in past.
6. Patients who are on medications which can cause optic neuropathy.

Methods

All patients of newly diagnosed pulmonary TB on standard HRZE regimen were examined thoroughly before initiating ATT and thereafter every month up to 6 months during a period of one year. Socio demographic data with patient's personal identification information was recorded. Detailed clinical history including dietary habit, addiction to tobacco, alcohol, any other medication, any ocular trauma or surgery was noted. External examination of eyes and pupillary reflex were noted on torch light examination. All the patients were evaluated for best corrected visual acuity by illuminated Snellen chart for 20 feet distance. Visual acuity loss was counted if it had exceeded two lines in Snellen chart between each monthly ophthalmic examination in the absence of other causal factors. Colour vision was assessed using Ishihara chart. Subjects were tested while wearing best correction.

Detailed fundus examination was done with indirect ophthalmoscope and slit lamp bio microscopy with +78D lens (Volk) for posterior segment pathology. Visual field testing was done using the Carl Zeiss Meditec HFA 2 Humphrey field analyzer with 30-2 threshold programme, with dim ambient light source with full refractive correction. Examination was repeated until reliable fields were obtained. Only those fields that were reliably performed were included in the analyses. All participants were called every month for follow up detailed ophthalmic examination up to 6 months.

Statistical analysis

The Chi-square test was applied to compare statistical difference in visual function among tuberculosis patients before and after initiating of ATT. The P value equal to or less than 0.05 was considered statistically significant.

Results

A total 160 eyes of 80 study participants were analyzed. Mean age of the patients is 32.56 year with maximum number of patients being in age group 18-30 years (56.25%). There were 45 (56.25%) males and 35 (43.75%) females (table 1).

Table 1: Demographic profile of patients

Demographic profile	No. of patients (N=80)	Percentage
Age (yrs)		
18-30 yrs	45	56.25%
31-50 yrs	25	31.25%
>50 yrs	10	12.50%
Mean±SD	32.56±3.22	
Sex		
Male	45	56.25%
Female	35	43.75%

Out of 160 eyes of 80 participants, 152 eyes of 76 patients had best corrected visual acuity of 20/20 on baseline examination while 8 eyes of four patients had baseline best corrected visual acuity ranging from 20/30 to 20/60; which was found to be due to cataract in these patients. Thus baseline best corrected visual acuity was ranged from 20/20 to 20/60. All the patients were followed up at monthly interval up to 6 months and their visual acuity was tested, during which we found that decline in visual acuity from baseline was seen in 12 eyes of six patients (7.5%) in which 2 eyes of one patient had drop in visual acuity at 4th month follow up, 8 eyes of four patients had drop in visual acuity at 5th month follow up and 8 eyes of four patient at 6th month follow up (table 2).

Table 2: Visual acuity changes from baseline in participants during six month follow up study

Visual acuity	20/20	<20/20 to 20/60	<20/60 to 20/200	<20/200
Baseline	152 (95%)	8 (5%)	0	0
1st month	152 (95%)	8 (5%)	0	0
2nd month	152 (95%)	8 (5%)	0	0
3rd month	152 (95%)	8 (5%)	0	0
4th month	148 (92.5%)	10 (6.25%)	2 (1.25%)	0
5th month	140 (87.5%)	12 (7.5%)	8 (5%)	0
6th month	138 (86.25%)	14 (8.75%)	8 (5%)	0

Baseline colour vision was found to be normal in 160 eyes of 80 study participants. Colour vision was assessed using Ishihara colour vision plates. During study, it was observed that out of 160 eyes, 10 eyes of five patients (6.25%) showed colour vision abnormality at the end of 6 month follow up. These differences in colour vision status between baseline and at the end of 6th month from baseline (p=0.001, Chi square value is 11.52) were statistically significant (table 3).

Table 3: Colour vision changes in study participants during six month follow up

Colour vision	No. of eyes (N=160)	Percentage
Baseline	0	0%
1st month	0	0%
2nd month	0	0%
3rd month	0	0%
4th month	4	2.5%
5th month	6	3.75%
6th month	0	0%
Total no of New eyes affected	10	6.25%

No visual field changes were found on baseline evaluation in all 160 eyes. At the end of six month follow up study 10/160 (6.25%) eyes developed changes in their visual fields from baseline. Out of 10 eyes, four eyes had developed changes at 4th month follow up and six eyes had developed changes at 5th month follow up. The most common defect seen was cecocentral scotoma in four (2.5%) eyes out of 160 eyes. Other defects seen were peripheral constriction (2.5%) and peripheral defect in different quadrant (1.25%) (Table 4).

Table 4: Visual field changes from baseline in study participants during six month follow up

Visual field changes	Cecocentralscotoma	Peripheral constriction	Peripheral defect in different quadrants	Bitemporal hemianopia
Baseline	0	0	0	0
1st month	0	0	0	0
2nd month	0	0	0	0
3rd month	0	0	0	0
4th month	0	4 (2.5%)	0	0
5th month	4 (2.5%)	0	2 (1.25%)	0
6th month	0	0	0	0
Total no. of eye affected			10 (6.25%)	

Discussion

Given the increasing prevalence of tuberculosis, antitubercular drugs frequently used are also associated with ocular toxicity. Ethambutol is the most commonly implicated drug. It is generally well tolerated, but known to cause optic neuritis, more specifically retro bulbar neuritis causing blurred vision, decreased visual acuity, central scotomas, and loss of red-green color vision. The exact mechanism of toxicity is not understood. Polak BC et al had reported that Ethambutol causes optic neuropathy in 1-5% of patients using antituberculous medications[11]. Clarke et al in 1972 stated that a cumulative dose of 150 g is considered critical dose for ethambutol toxicity[12]. Citron observed that optic nerve toxicity developed usually after two months of therapy[8]. This was also evident in present study.

In our study colour vision was tested with Ishihara pseudo isochromatic colour vision test while in Garg P et al study colour vision was tested using both Ishihara and Farnsworth D-15 colour vision test[13]. In the study; 128 eyes of 64 patients of category 1 and 2 were evaluated, of which colour vision abnormalities were noted in 16 eyes of eight patients (p value= 0.003).Since present study was done using Ishihara colour plates, the subtle colour vision defects may not be detected.

No visual field changes were found on baseline evaluation in all 160 eyes. At the end of six month follow up study 10/160 (6.25%) eyes developed changes in their visual fields from baseline. Out of 10 eyes, four eyes had developed changes at 4th month follow up and six eyes had developed changes at 5th month follow up. The most common defect seen was cecocentral scotoma in four (2.5%) eyes out of 160 eyes. Other defects seen were peripheral constriction (2.5%) and peripheral defect in different quadrant (1.25%). Bharamshetter RS conducted a study in which160 eyes of 80 patients who were started on ATT under RNTCP were analyzed[14]. Visual field defects were seen in 10 (6.25%) eyes out of 160 eyes, in which (40%) had centrocecal defects, (40%) central defect, (20%) had paracentral defects and (20%) had nerve fiber defect.

In Mahrukh et al study, 198 eyes of 100 patients (two patients were one eyed) were analyzed and at the end of two months of ATT[15]. It was seen that 27/198 (13.63%) eyes developed changes in their visual fields. The most common defect seen was the peripheral defects in different quadrants (8.1%). Other defects seen were peripheral constriction of the isopter (3.03%), central scotoma (1.01%) and bitemporal hemianopia (1.01%). Garg P[13] also noted in his study that four patients had developed field defects (6.3%) after 2 months of ATT.

There is not a single simple diagnostic test that can be confirming or diagnostic for ATT toxicity. For our patients, the diagnosis EMB ocular toxicity was based on new onset of ocular symptoms compatible with ATT-related toxicity such as diminished visual acuity from baseline, altered colour vision perception, development of visual field defects and lack of an alternative explanation for the new ocular symptoms.

Conclusion

We found that ocular toxicity was seen in a significant number of patients (6.25%). The ocular toxicity of ethambutol in our patients had manifested in the form of changes in visual acuity, colour vision, visual field and fundoscopy picture. We conclude that mandatory ophthalmic examination using sensitive indicators at monthly intervals is paramount and that, along with discontinuation of the offending drug when possible, constitutes the basis of treatment of drug-induced optic neuropathy in such patients

References

1. Kanabus A. Information about Tuberculosis, Global Health Education; 2018. Available from: www.tbfacts.org.
2. International Standards for Tuberculosis Care, 3rd edition, 2014, http://www.who.int/tb/publications.
3. B. E. Gülbay, Ö. U. Gürkan, Ö. A. Yildiz et al., "Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis," Journal of Respiratory Medicine, 2006; 100(10): 1834–1842.
4. R. Singla, S. K. Sharma, A. Mohan et al., "Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity , Indian Journal of Medical Research, 2010; 132(7):81–6.
5. J. Volmink and P. Garner, "Directly observed therapy for treating tuberculosis," Cochrane Database of Systematic Reviews, 2007; 4, Article ID CD003343.
6. Carr RE, Henkind P. Ocular manifestations of ethambutol: Toxic amblyopia after administration of an experimental antituberculosis drug. Arch Ophthalmol. 1962;67:566–71.
7. Kokkada SB, Barthakur R, Natarajan M, Palaian S, Chhetri AK, Mishra P, et al. Ocular side effects of antitubercular drugs-a focus on prevention, early detection and management. Kathmandu Univ Med J (KUMJ). 2005;3(4):438–41.
8. Citron KM, Thomas GO. Ocular toxicity from ethambutol. Thorax. 1986;41(10):737–9.

9. Makunyane P, Mathebula S. Update on ocular toxicity of ethambutol. Afr Vis Eye Health. 2016;75:1–4.
10. Preventive measures against drug-induced ocular toxicity during antituberculous treatment (general recommendations). Annual Report. Hong Kong: Department of Health; 2002. 8. Muntingh GL. Drug and Contact Lens Interactions. South Afr Family Pract. 2005;47:24–8.
11. Polak BCP, Leys M, van Lith GHM. Blue-Yellow Colour Vision Changes as Early Symptoms of Ethambutol Oculotoxicity. Ophthalmol. 1985;191(4):223–6.
12. Clarke GBM, Cuthbert J, Cuthbert RJ, Lees AW. Isoniazid plus ethambutol in the initial treatment of pulmonary tuberculosis. Br J Dis Chest. 1972;66:272–6.
13. Garg P, Garg R, Prasad R, Mishra AK. A prospective study of ocular toxicity in patients receiving ethambutol as a part of directly observed treatment strategy therapy. Lung India. 2015;32(1):16–29.
14. Bhramshetter RS. Visual Field defects in patients of tuberculosis on ethambutol. J Evid Based Med Health Care. 2017;4(3):1323–7.
15. Mahrukh AA, Mohd B, A. Visual field changes in patients receiving antitubercular drug therapy at tertiary care hospital: an analytical observational study. Int J Contemp Med Res. 2017; 4(2):346–9.

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