

OCULAR MORBIDITY IN PATIENTS ON ANTI TUBERCULOSIS TREATMENT

Ophthalmology

Dr. Prerna Vilas Meshram

MBBS, DOMS, DNB Ophthalmology.

Dr. Minu Ramakrishnan

MBBS, DO, DOMS, DNB Ophthalmology.

ABSTRACT

Introduction: India is among the countries that carry the highest burden for tuberculosis. Antitubercular drugs (ATT) are frequently associated with ocular toxicity. Among ATT drugs, ethambutol is the most commonly implicated drug causing optic neuropathy. For assessing spectrum of ATT induced ocular toxicity, clinical presentation and monitoring, a cross-sectional observational study was conducted. **Materials And Methods:** Newly diagnosed drug susceptible pulmonary tuberculosis patients on first line antituberculosis treatment referred to ophthalmology OPD during a study period from March 2022 - March were included in the study. Detailed history, best corrected visual acuity, color vision test, optic disc changes and visual fields were carried out in all patients. **Results:** Out of 91 study patients, 48 patients (26.4%) had drop in visual acuity $< 6/12$ (p value is < 0.05). Total 16 eyes of eight patients (8.8%) developed colour vision abnormality (p value < 0.0001) and 18 eyes of nine patients (9.9%) had optic disc changes (p value < 0.0001). Visual field defects were noted in 20 eyes of ten patients (11%) eyes (p value = 0.1). **Conclusion:** Present study observed that one in ten cases on ATT suffers from ocular morbidity. Besides a decrease in visual acuity, colour vision abnormalities, decrease in peripheral field vision and optic disc abnormalities were observed in these patients. A significant association was observed between presence of these abnormalities (p value < 0.0001) with increased duration of treatment.

KEYWORDS

Antitubercular drugs, fansworth D15, optic neuropathy, perimetry.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by mycobacterium tuberculosis [1]. TB is a significant public health concern, contributing substantially to illness and death. In 2017, despite advancements in diagnostic and treatment methods, there were nearly ten million newly reported TB cases, resulting in an estimated 1.6 million TB-related deaths worldwide. A substantial proportion of the global population, approximately one-quarter, carries latent TB infections, which means they are at risk of developing active TB disease at some point in their lives [2].

Ethambutol is one of four first-line drugs used to treat TB [3].

Ethambutol hydrochloride is a primary antitubercular drug prescribed during the initial ethambutol can lead to optic neuropathy, with incidence rates ranging from 0.5% to 63%. [4]

The toxicity associated with ethambutol is depends on both the dose and duration of therapy. Incidence rates is around 18% with higher doses (> 35 mg/kg/day), 5%–6% with moderate doses (25 mg/kg/day), and less than 1% with lower doses (15 mg/kg/day) during a treatment duration of at least 2 months. Early detection and discontinuation of the drug can reverse the toxicity, but visual damage may be irreversible. [4]

Ethambutol (EMB) is the most commonly used antitubercular drug known to cause optic neuropathy, blurred vision, decreased visual acuity, central scotoma and loss of red-green colour vision [5].

EMB toxicity depends on the dose and duration of treatment and in most of the cases it is reversible, but sometimes become irreversible leads to permanent visual impairment. It has been said that there is no so-called “safed dosage” for EMB. [6]

AIM AND OBJECTIVES

AIM

To estimate the incidence and types of ocular morbidity in patients on anti-tuberculosis treatment (First line ATT)

OBJECTIVES

1. To assess the visual functions (visual acuity, colour vision) in patients on anti-tuberculosis treatment.
2. To record their ocular findings and analyse their visual fields with perimetry (30-2).
3. To assess colour vision with Fansworth D-15 test.
4. To analyse visual impairment in relation to the duration of anti-tuberculosis treatment.

MATERIAL AND METHODS

Study Area

Department Of Ophthalmology, K. J. Somaiya Medical College and Research Centre, Mumbai.

Study Population

All the diagnosed cases of Primary Pulmonary Tuberculosis on First line ATT who presented to department of Ophthalmology in K.J. Somaiya Medical College And Research Centre, Mumbai

Study Design

A Cross sectional Observational study.

Sample Size Calculation:

The sample size was calculated using following formulae:
 $n = 4pq / l^2$

n- Sample size

4= z value at 95% confidence level.

q=(100-p) i.e, 100-6=94%

p- Taken as 6% (prevalence of ocular morbidities in ATT cases)

l- Absolute error (taken as 5%)

$n = 4 \times 6 \times 94 / 5 \times 5$

n- 91 (approx.) sample size.

Study Duration

1 Year (March 2022 to March 2023)

Inclusion Criteria

1. All diagnosed cases of pulmonary TB on ATT Treatment. Standard HRZE ATT regime (H = isoniazid, R = rifampicin, Z = pyrazinamide, E = Ethambutol) followed H: 4-6 mg/kg body weight, R: 8-12 mg/kg body weight, Z: 20-30 mg/kg body weight, E: 15-25 mg/kg body weight.
2. Adult patients (age > 18 years)
3. Those who gave informed written consent to participate in the study were included.

Exclusion Criteria

1. Major systemic illness (Diabetes mellitus, renal disease, demyelinating disease).
2. Pre-existing posterior segment pathology affecting visual acuity.
3. Any dense ocular media opacity.
4. Pre-existing colour vision defects & medications that can affect colour vision like oral contraceptives, digoxin, indomethacin.
5. Medications which can cause optic neuropathy like phosphodiesterase type 5 (PDE-5) inhibitors and amiodarone.

Methods

Study was conducted in accordance to the ethical principles (ethics committee approval). Patients were explained about the study being performed and a written informed consent was obtained from all the patients. Approval to use their medical records and re-evaluate each case was taken. All patients presenting to Department of Ophthalmology were examined for ocular side effects as a result of ATT.

Clinical Assessment

- History of present complaints
- Past History, duration of treatment.
- History of Anti TB Treatment
- Detailed clinical history including dietary habit, addiction to tobacco, alcohol.
- Any other medication, any ocular trauma or surgery.

Ocular Examination

- Best corrected visual acuity by illuminated Snellen chart for 6 metres distance.
- Colour vision was assessed using Farnsworth's D15.
- IOP using Goldmann applanation tonometer.
- Slit lamp biomicroscopy for anterior segment evaluation with +78D lens (Volk) for posterior segment pathology
- Detailed peripheral fundus examination with indirect ophthalmoscope
- Visual field (30-2) testing was done using the Carl Zeiss Meditec HFA 2 Humphrey field analyzer.

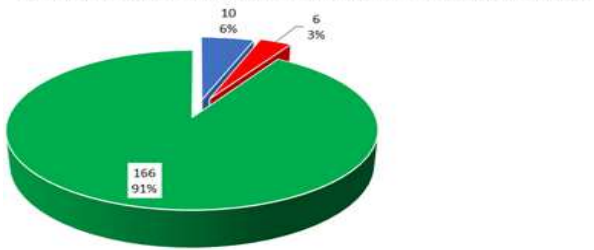
Statistical Analysis

All the data was noted down in a pre-designed study proforma. Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test. Quantitative data was represented using Mean ± SD. Analysis of Quantitative data between the two groups was done using unpaired t-test if data passed 'Normality test' and by Mann-Whitney Test if data failed 'Normality test'. A p-value < 0.05 was taken as level of significance. Results were graphically represented where deemed necessary. SPSS Version 26.0 was used for most analysis and Microsoft Excel 2021 for graphical representation.

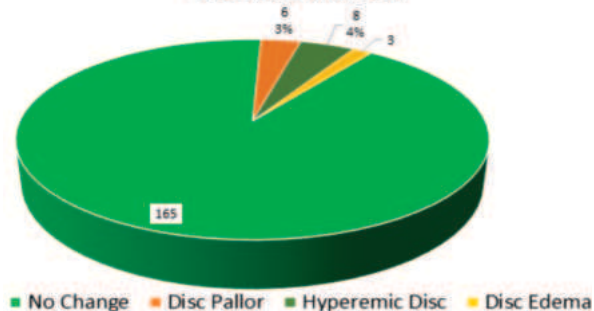
Table 1. Distribution Of Study Groups As Per Visual Acuity

Visual Acuity	Out of 182 eyes	%
6/6-6/9	134	73.7%
6/12-6/36	44	24.1%
<=6/60	4	2.2%
Total	182	100.0%

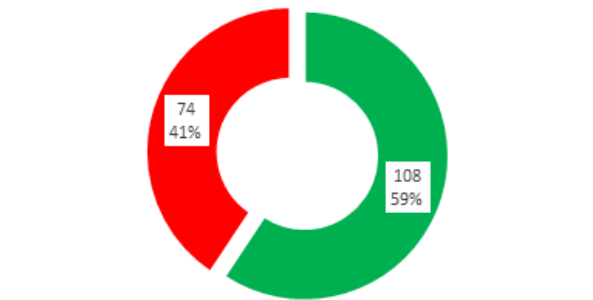
Pie diagram showing distribution of D 15 Color vision amongst study group



Pie diagram showing distribution of Optic Disc Changes amongst study subjects (Total Eyes)



Pie diagram Showing distribution of eyes according to ATT duration



Pie diagram showing distribution of Visual Field Analysis amongst study Participants (both eyes)

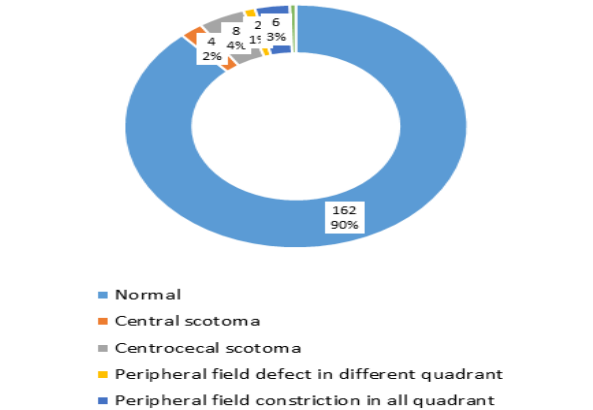


Table 2. Association Of Duration Of ATT With Visual Field Changes.

ATT Duration		Visual Field Analysis		Total	Test statistics
		Abnormal	Normal		
3 to 6 months	Count	9	99	108	Chi square = 2.673 DF=1 P value = 0.102 (P > 0.05 / 0.01)
	Column %	8.3%	91.7%	100.0%	
	Residual	-3.5	3.5		
>6months	Count	12	62	74	
	Column %	16.2%	83.8%	100.0%	
	Residual	3.5	-3.5		
Total	Count	21	161	182	
	Column %	11.5%	88.5%	100.0%	

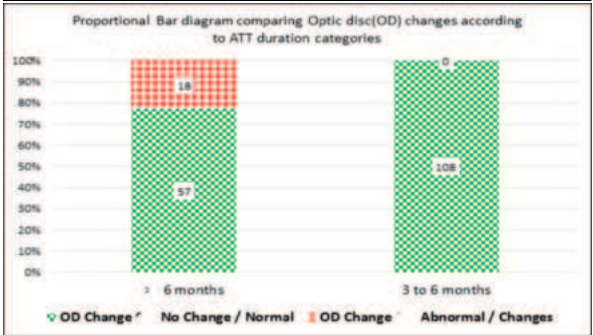


Table 3. Association Of Duration Of ATT With Optic Disc Changes.

Duration of ATT category		Optic Disc Changes		Total
		Abnormal / Changes	Normal / No change	
3 to 6 months	Count	0	108	108
	Column %	0.0%	100.0%	100.0%
	Residual	-10.1	10.1	

> 6 months	Count	18	57	74
	Column %	23.0%	77.0%	100.0%
	Residual	10.1	-10.1	
Total	Count	18	164	182
	Column %	9.3%	90.7%	100.0%

RESULT

Initially 92 patients of newly diagnosed drug susceptible pulmonary tuberculosis were examined. Out of 92 study participants, one participant had retinitis pigmentosa, hence excluded. Thus total 182 eyes of 91 study participants were analysed Mean age of the patients is 32 years with maximum number of patients being in age group ≤ 20 years (27.5%).

There were 56 (61.50 %) males and 35 (38.50%) females.

Out of 182 eyes of 91 participants, 134 eyes (73.60%) had best corrected visual acuity of 6/6 -6/9 using Snellen visual acuity chart ,whereas 48 eyes (24.2%) had best corrected visual acuity ranging from 6/12 -6/36, 4 eyes (2.2%) had best corrected visual acuity ranging from $\leq 6/60$ (p value is <0.05).

Out of 182 eyes of 91 patients, Colour vision was assessed using FANSWORTH D -15. During study, it was observed that ,16 eyes of 8 patients (8.8%) showed acquired colour vision defect.

Out of which 10 eyes of 5 patients (5.5%) showed PROTON DEFECT 6 eyes of 3 patients (3.3%) showed TRITAN DEFECT . Results were statistically significant (p value is 0.0001).

Out of 182 eyes of 91 patients ,160 eyes were normal 20 eyes had developed visual field changes The most common defect seen was centrocecal scotoma in 8 eyes of 4 patients (4.4%) , 4 eyes of 2 patients(2.2%) developed central scotoma. Other defects seen were peripheral field constriction in 6 eyes of 3 patients (3.3%), peripheral defect in different quadrant in 2 eyes of 1 patient (1.1 %). These differences in visual field defects (p value is 0.1).

It was observed that among 182 eyes of 91 patients,18 eyes had developed optic disc changes.In which 8 eyes of 4 patients (4.4%) had hyperemic disc,6 eyes of 3 patients (3.3%) had disc pallor .

4 eyes of 2 patients (2.2 %) had disc edema (P value = 0.0001) were statistically significant.

It was observed that the proportion of abnormal colour vision is higher in patients on ATT Duration > 6 Months compared to patients on ATT Duration of 3 to 6 Months (P value = 0.0001) which is < 0.05 or 0.01 and is statistically significant.

The proportion of abnormal Visual Field analysis (ATT Duration 3 to 6 months) Is more or less same compared to second category (ATT Duration > 6 Months) means statistically insignificant.(P value = 0.102)which is > 0.05 or 0.01.

The proportion of abnormal Optic Disc changes is higher in ATT Duration > 6 Months compared to ATT Duration 3 to 6 Months (P value = 0.0001) which is < 0.05 or 0.01 and is statistically significant.

DISCUSSION

Ethambutol is being used to treat tuberculosis since the 1960s. Leibold JE et al reported the incidence of ethambutol toxicity depending on dosage. Citron observed that optic nerve toxicity developed usually after two months of therapy. This was also evident in present study.

In our study colour vision was tested with and FarnsworthD-15 colour vision test while in Solu TM study colour vision was tested with Ishihara colour vision test. In the study in which 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).In our study ,out of 16 eyes , 10 eyes of 5 patients showed impairment in red-green colour perception and 6 eyes of 3 patients impairment in blue-yellow colour perception (p value < 0.0001). All abnormalities were noted by Farnsworth Panel D-15 test.

In our study 20/182 (5.5%) eyes developed visual field defects, in which the most common defect seen was centrocecal scotoma (4.4%), central scotoma (2.2 %) second most common visual field defects (p

value =0.1). Bharamshetter RS conducted a study in which 160 eyes of 80 patients .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.It was concluded in study that the field defects were dose dependent ,statistically significant at the level of $p<0.001$.

In present study,Out of 182 eyes Optic disc changes were seen in 18 eyes in which, 8 eyes of 4 patients had hyperemic disc,6 eyes of 3 patients had disc pallor and 4 eyes of 2 patient had disc edema (p value is 0.0001) were statistically significant Common disc changes seen were disc hyperemia, pallor and edema. ,while in study conducted by Pragati Garg and Trupti M optic disc changes were observed as 4.7% and 5.3%.

For our patients, the diagnosis EMB ocular toxicity was based on new on set of ocular symptoms . These all three parameters of optic nerve function were taken into account for clinical diagnosis.

CONCLUSION

Present study observed that one in ten cases on ATT suffers from ocular morbidity. Besides a decrease in visual acuity, color vision abnormalities, decrease in peripheral field vision and optic disc abnormalities were observed in these patients. A significant association was observed between presence of these abnormalities with increased duration of treatment. Educating patients about toxicity of Antitubercular drugs is a crucial factor in treatment of tuberculosis and ocular examination is important to identify significant morbidity and decide on further line of management.

REFERENCES

- Dartois, V.A., Rubin, E.J. Anti-tuberculosis treatment strategies and drug development: challenges and priorities. *Nat Rev Microbiol* 20,(2022) 685–701.
- Ashtosh N. Aggarwal, Quality of life with tuberculosis, *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, Volume 17, 2019, 100121, ISSN 2405-5794.
- MacVinish, S., McMaster, D., Moledina, T. *et al*. Ethambutol and visual assessment in England: current practice and recommendations. *Eye* (2023).
- Bandyopadhyay S, Banerjee S, Bandyopadhyay SK, Shanthanath M C, Biswas S. A prospective evaluation of ocular toxicity in patients receiving ethambutol as anti-tubercular therapy. *Sudanese J Ophthalmol* 2020;12:12-6
- IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 19, Issue 8 Ser.10 (August. 2020), PP-09-13
- Mahrukh AA, Bhat MA. Visual field changes in patient receiving antitubercular drug therapy at tertiary care hospital: An analytical observational study. *Int J Contemp Med Res* 2017;4:346-9.
- Mandal, Sohini, et al. "Prospective study to evaluate incidence and indicators for early detection of ethambutol toxicity." *British Journal of Ophthalmology* 105.7 (2021): 1024-1028.
- Pai, Madhukar, and Prabhat Jha. "Tuberculosis in India: health policy alone is not enough—Authors' reply." *The Lancet* 389.10088 (2017): 2471-2472.
- Thakur, Gargi, Shalvi Thakur, and Harshad Thakur. "Status and challenges for tuberculosis control in India—Stakeholders' perspective." *Indian Journal of Tuberculosis* 68.3 (2021): 334-339.
- Varshney K, Patel H, Kamal S. Trends in Tuberculosis Mortality Across India: Improvements Despite the COVID-19 Pandemic. *Cureus*. 2023 Apr 29;15(4):e38313.
- Dhamnetiya, D., Patel, P., Jha, R.P. *et al*. Trends in incidence and mortality of tuberculosis in India over past three decades: a joinpoint and age-period-cohort analysis. *BMC Pulm Med* 21, 375 (2021).
- Madkour MM, Al-Otaibi KE, Al Swailem R. Historical Aspects of Tuberculosis. In *Tuberculosis*. Springer Berlin Heidelberg. 2004;pp.5-30.
- Iademarco MF, Castro KG. Epidemiology of tuberculosis. In *Seminars in respiratory infections* 2003;18(4):225-240.
- Bates JH. Diagnosis of tuberculosis. *CHEST Journal*. 1979 Dec 1;76(6 Supplement):757-63.
- Jenkins PA. The microbiology of tuberculosis. *Clinical Tuberculosis*. 1994;34-41.
- TB disease in India: age group distribution, 2003. *Tuberculosis control in India*. Chapter 1:1.
- Ragini Ghiya, Eknath Naik, Beata casanas, Ricardo Izurieta, Yogesh Marfatia. Clinico-epidemiological profile of HIV/TB co infected patients in Vadodra, Gujarat. *Indian Journal of Sexually transmitted Diseases and AIDS* 2009; 30 (1): 10-15.
- Nigisch A, Glawischnig W, Bagó Z, Greber N. *Mycobacterium caprae* Infection of Red Deer in Western Austria—Optimized Use of Pathology Data to Infer Infection Dynamics. *Front Vet Sci*. 2018;5:350.
- Sharma SK, Mohan A, Kadhiravan T. HIV-TB co-infection: epidemiology, diagnosis & management. *Indian J Med Res*. 2005 Apr 1;121(4):550-67.
- Chaudhuri AD. Recent changes in technical and operational guidelines for tuberculosis control programme in India - 2016: A paradigm shift in tuberculosis control. *J Assoc Chest Physicians* [2023 Mar 7];5:1-9.
- Aggarwal R, Sethi P, Duvesh RK, Sethi HS, Naik M, Rai HK. Ocular toxicity of Anti-Tubercular Drugs. *DJO* 2021;31:35-38.
- Campbell IA, Ormerod LP. Ethambutol and the eye [letter]. *Lancet* 1988;9:113-4.
- Schild H Fox. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med*. 1991;90:404-6. PMID: 1848398
- Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. *Mayo Clin Proc*. 2003;78(11):1409–1411.
- Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax*. 1986;41:737–739.
- Chatterjee VKK, Buchanan DR, Friedmann AI, Green M. Ocular toxicity following ethambutol in standard dosage. *Br J Dis Chest*. 1986;80:288–290.
- Kho RC, Al-Obailan M, Arnold AC. Bitemporal visual field defects in ethambutol-induced optic neuropathy. *J Neuroophthalmol* 2011;31:121–126.