Original Article

DOI: 10.7860/JCDR/2021/51451.15792

Ocular Manifestations among Newly Diagnosed Tuberculosis Patients Receiving Anti-Tubercular Therapy under Revised National Tuberculosis Control Programme: A Prospective Cohort Study

Internal Medicine Section

SOUMYA RAY[1], TA RUPAM KUMAR[2], PALLABI RAYCHAUDHURI[3], UTTAM BISWAS[4], MOUSUMI BANDYOPADHYAY[5]

ABSTRACT

Introduction: Ocular tuberculosis has diverse presentations. As microbiological confirmation is difficult, a high index of suspicion is required. The present study replenishes the gap of existing knowledge regarding ocular tuberculosis and facts related to antitubercular drug related toxicity.

Aim: To evaluate the magnitude and outcome of ocular tuberculosis along with antitubercular drug related ocular toxicity, with special reference to ethambutol toxicity.

Materials and Methods: This cohort study was conducted from May 2018 to April 2019 at Outpatient Department of Ophthalmology, Burdwan Medical College and Hospital, West Bengal, India. Total 170 newly diagnosed tuberculosis patients underwent comprehensive ophthalmic examination for any signs of ocular tuberculosis or development of antitubercular drug related ocular toxicity. They were treated and followed up to the completion of Anti-Tubercular Therapy (ATT). The statistical software Statistical Package for the Social Sciences (SPSS) version 20.0 was used for the analysis.

Results: Out of total 170 study participants, 110 (64.7%) were male, mean age was 35.65±15.49 years. Ocular tuberculosis was found in 12 (7.05%) patients. Four patients had choroidal tuberculoma, two had Eales disease, four had choroiditis, two had anterior and intermediate uveitis. All the ocular tubercular lesions responded to ATT. Total 7 (4.1%) patients developed ethambutol-induced ocular toxicity. Following stoppage of ethambutol and treatment with corticosteroids there was significant improvement in colour vision, perimetry and Visual Evoked Potential (VEP) findings in 3 (42.9%) patients. Unfortunately, 4 (57.1%) patients developed optic atrophy.

Conclusion: Comprehensive ophthalmic examination should to be done in all tuberculosis patients to detect and treat co-existing ocular tuberculosis as well as early detection of antitubercular drug toxicity. Withholding of the offender can result in visual recovery.

Keywords: Choroidal tuberculoma, Ethambutol toxicity, Eales disease, Ocular tuberculosis, Uveitis

INTRODUCTION

In primary ocular tuberculosis, the eye is the initial portal of entry into the body, while the secondary one is defined as an infection resulting from contagious spread from an adjacent structure or haematogenous dissemination.

Primary infection of the eye is rare. Secondary ocular tuberculosis is the ocular involvement as a result of haematogenous spread from a distant site or a direct invasion from adjacent areas like the sinus or the cranial cavity. Almost every tissue of the eye and its adnexa can get affected. Ocular tuberculosis may be acute but usually it runs a chronic course with exacerbations and remissions [1]. Involvement of ocular tissue in tuberculosis can also be due to hypersensitivity reactions [2].

Ethambutol is the most commonly implicated antitubercular drug known to cause optic neuropathy more specifically retrobulbar neuritis causing blurred vision, decreased visual acuity, central scotoma and loss of red-green colour vision through its possible zinc chelating effect and toxic damage in retinal ganglion cells [3]. Though it is reversible on prompt discontinuation, still permanent visual impairment reported in literature [4].

To diagnose the ocular side effects of antitubercular drugs careful recording of visual acuity is essential. Drop in visual acuity varies greatly from nil to minimally reduced to no light perception [5]. The colour vision abnormality and contrast sensitivity is the earliest changes that appear in ethambutol toxicity. Among visual field changes mostly central scotoma although bitemporal field defects and peripheral field constriction can occur [6].

The P-100 latency value is used as an early indicator of Visual Evoked Potential (VEP) abnormality for ethambutol induced ocular toxicity [7]. Immediate discontinuation of ethambutol is only effective management as it can halt the progressive vision loss and allow effective recovery in due course of time. High-dose methylprednisolone accelerates recovery of the visual function. These recommendations are valid only for demyelinating retrobulbar-neuritis [8].

The study was conducted with the objective to estimate the proportion of ocular tuberculosis along-with its response to Anti-Tubercular Therapy (ATT) and also to estimate the occurrence of ethambutol toxicity with special reference to its reversibility following treatment.

MATERIALS AND METHODS

This cohort study was conducted from May 2018 to April 2019 at Outpatient Department of Ophthalmology, Burdwan Medical College and Hospital, West Bengal, India. Approval from Institutional Ethics Committee (bearing Memo no. BMC-2972, dated- 28.12.2017) and informed consent from all participants were obtained.

Inclusion criteria: All newly diagnosed tuberculosis patients registered (irrespective of organ of involvement) within the time frame of six months (May 2018 to October 2018) were included in the study. Rest six months of study period was reserved for follow-up visits and data analysis. In the above mentioned time frame 170 newly diagnosed tuberculosis patients were registered at Revised National TB Control Programme (RNTCP) of Burdwan Medical College and Hospital (irrespective of organ of involvement).

Exclusion criteria: Non ambulatory patients, with co-existing other infectious diseases like Human Immunodeficiency Virus (HIV) and leprosy or patients with previously treated for retina and choroidal disorders (like photocoagulation, vitrectomy, intravitreal steroids) were excluded from the study.

Case definition of ocular TB: As per the standard guideline laid by Central TB Division and Indian Council of Medical Research (ICMR) [9] ocular tuberculosis can be of three types:

A) Possible ocular TB: Patients with the following (1, 2 and 3 together or 1 and 4) are diagnosed as having possible ocular TB:

1. At least one clinical sign suggestive of ocular TB (see presumptive ocular TB), and other aetiology excluded
2. X-ray/Computed Tomography (CT) chest not consistent with TB infection and no clinical evidence of extraocular TB.
3. At least one of the following: Documented exposure to TB and/or immunological evidence of TB infection.
4. Molecular evidence of Mycobacterial tuberculosis infection.

B) Clinically diagnosed ocular TB: Patients with all the following (1, 2 and 3 together) are diagnosed as having probable ocular TB:

1. At least one clinical sign suggestive of ocular TB (as presumptive ocular TB stated below), and other aetiologies excluded
2. Evidence of chest X-ray consistent with TB infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites
3. Documented exposure to TB and/or immunological evidence of TB infection.

C) Bacteriologically confirmed ocular TB: A patient with at least one clinical sign of ocular TB, along with microbiological (smear/culture) or histopathological confirmation of mycobacterium tuberculosis from ocular fluids/tissues.

Presumptive ocular TB signs: A patient with one of the following clinical presentations- Granulomatous anterior uveitis/non granulomatous anterior uveitis, not associated with any other known clinical entity, e.g., HLA-B27/intermediate uveitis, with/without healed/active focal lesions/posterior uveitis, including subretinal abscess, choroidal/disc granuloma, multifocal choroiditis, retinal periphlebitis and multifocal serpiginous choroiditis/pan-uveitis rarely, scleritis (anterior and posterior), interstitial and disciform keratitis.

All tuberculosis patients received ATT as per guidelines of RNTCP i.e., Isoniazid (450 mg), Rifampicin (600 mg), Ethambutol (1600 mg) (both in the intensive phase and continuation phase) and Isoniazid (450 mg), Rifampicin (600 mg), Ethambutol (1600 mg) and Pyrazinamide (2000 mg) (only in the intensive phase) [10].

Procedure

All tuberculosis patients (irrespective of organ involvement) underwent visual acuity test with Snellen's opto type self-illuminated drum, slit lamp examination and fundus examination by indirect ophthalmoscopy. If the ocular manifestations corroborate with the findings of presumed ocular tuberculosis, then the researchers excluded the other possibilities like blood investigation for Toxoplasma, Rubella, Cytomegalovirus, Herpes (TORCH), Human Leukocyte Antigen- B27 (HLA-B27), Venereal Disease Research Laboratory (VDRL) test for syphilis and test for Human Immunodeficiency Virus (HIV) antibody. Finally, the magnitude of ocular TB was worked out. Mantoux test was performed in all the suspected ocular tuberculosis patients in whom no extra-ocular tuberculosis was found. According to severity of ocular signs and symptoms patients were undergone Fundus Fluorescein Angiography (FFA) to determine the activity of ocular lesion in the posterior segment. Ocular tuberculosis patients were followed-up at six months and till completion of ATT for the treatment response.

In the follow-up visits, patients were subjected to similar examination as done in the first visit. Patients of ocular tuberculosis were also checked for response to the ATT by comparing with baseline investigation data and performing FFA.

All study participants were also checked for ocular toxicity of antitubercular drugs. If ocular toxicity was suspected by deterioration of visual acuity, colour vision or contrast sensitivity score then automated perimetry and VEP were performed. And the patients were treated as per recommended guidelines. Ethambutol was stopped immediately and regimen modification was done. If retrobulbar neuritis is suspected then patients were admitted and intravenous (i.v.) methyl prednisolone given as per dosage regimen [11].

STATISTICAL ANALYSIS

The statistical software Statistical Package for the Social Sciences (SPSS) version 20.0 was used for the analysis. Here, categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi-square test for Independence of Attributes/Fisher's-Exact Test as appropriate. Continuous variables are expressed as mean, median and standard deviation and compared over time using Wilcoxon Signed-Rank Test. An alpha level of 5% has been taken, i.e., if any p-value <0.05 it has been considered as significant.

RESULTS

Out of total 170 study participants 110 (64.7%) were males, mean age was 35.65±15.49 years [Table/Fig-1].

Age groups (years)	Frequency (%)	Sex		Types of tuberculosis	
		Males	Females	Pulmonary	Extra-pulmonary
≤10	3 (1.8%)	2	1	0	3
11-20	31 (18.2%)	20	11	23	8
21-30	44 (25.9%)	26	18	26	18
31-40	28 (16.5%)	21	7	22	6
41-50	33 (19.4%)	22	11	21	12
51-60	21 (12.4%)	13	8	10	11
61-70	7 (4.1%)	4	3	4	3
71-80	3 (1.8%)	2	1	2	1
Total	170 (100.0%)	110 (64.7%)	60 (35.3%)	108 (63.5%)	62 (36.5%)
		170		170	

[Table/Fig-1]: Demographic details of all study participants (N=170).

Total 12 (7.05%) patients were found to have ocular tuberculosis. Nearly half of ocular tuberculosis patients belonged to age group of 21-30 years. There was no sex predilection for ocular tuberculosis. It was found that ocular tuberculosis is significantly associated with extra-pulmonary tuberculosis [Table/Fig-2] and half of ocular tuberculosis patients had no concurrent extra-ocular tuberculosis [Table/Fig-3]. Various types of ocular tubercular lesions have been

Age		Sex		Association with types of tuberculosis		p-value for association with extra-pulmonary TB
Age group (years)	Frequency (%)	Males	Females	Pulmonary TB	Extra-pulmonary TB	
11-20	1 (8.33%)	1	0	0	1	<0.001
21-30	6 (50.0%)	3	3	1	5	
31-40	2 (16.67%)	1	1	0	2	
41-50	1 (8.33%)	1	0	0	1	
51-60	1 (8.33%)	1	0	0	1	
61-70	1 (8.33%)	0	1	1	0	
Total	12 (100.0%)	7 (58.33%)	5 (41.67%)	2 (16.67%)	10 (83.33%)	
		12 (100.0%)		12 (100.0%)		

[Table/Fig-2]: Distribution of ocular tuberculosis patients in relation to its age, sex and associations with types of tuberculosis (N=12).

presented in [Table/Fig-3]. All ocular tuberculosis patients without any extra-ocular tubercular lesions were Mantoux test positive.

Sl. No. of patients	Right eye	Left eye	Extra-ocular tuberculosis
1	Tubercular vasculitis	Serpiginous like choroiditis	Pulmonary TB
2	-	Vasculitis- Eales disease	Pulmonary TB
3	Choroidal tuberculoma Intermediate uveitis	Choroidal tuberculoma Intermediate uveitis	Nil
4	Anophthalmic	Multiple choroidal tubercles	Military tuberculosis
5	Vasculitis	Multifocal choroiditis	Nil
6	-	Choroidal tuberculoma	Spine TB
7	Multifocal choroiditis	Multifocal choroiditis	Nil
8	Anterior and Intermediate uveitis	Anterior and Intermediate uveitis	TB meningitis with bilateral occipital lobe infarction
9	Choroidal tuberculoma	Choroidal tuberculoma	TB Meningitis
10	Vasculitis- (Eales disease)	Vasculitis (Eales disease)	Nil
11	Serpiginous like choroiditis	-	Nil
12	Multifocal choroidits Anterior and Intermediate uveitis	Multifocal choroiditis	Nil

[Table/Fig-3]: Distribution of tuberculosis patients according to their presence of ocular lesions (n=12).
BL: Bilateral; RE: Right eye; LE: Left eye

Following treatment with ATT there was resolution of various tubercular lesions. [Table/Fig-4] shows the response of various tubercular lesions with ATT. There has been statistically significant resolution of intermediate uveitis (p-value=0.042), vasculitis (p-value=0.042) in right eye lesions. But tuberculoma and choroiditis in both the eyes did not resolve completely.

Eye lesions	At the time of diagnosis	At 6 months of ATT	At completion of ATT
Right eye			
Tuberculoma	2	2	2
Vasculitis	3	3	1
Intermediate uveitis	3	2	0
Choroiditis multifocal	2	2	2
Choroiditis serpiginous	1	1	1
Left eye			
Tuberculoma	4	4	4
Vasculitis	2	2	2
Intermediate uveitis	2	1	0
Choroiditis multifocal	3	3	3
Choroiditis serpiginous	1	1	1

[Table/Fig-4]: Distribution of right and left eye lesions with their response to Anti-Tubercular Therapy (ATT).

Seven out of 170 patients (4.1%) were suspected to be suffering from ethambutol induced ocular toxicity. The mean duration of ethambutol taken after which toxicity was first detected was 2.86±1.57 months. There was statistically significant fall in visual acuity at the time of detection of ethambutol toxicity. But after ethambutol withdrawal several patients recovered from their poor vision. Following withdrawal of ethambutol and regimen modification statistically significant number of improvements in colour vision, mean contrast sensitivity score (improves from 0.73 to 0.77) [Table/Fig-5], visual fields and in VEP findings, P-100 latency were statistically significant [Table/Fig-5]. But optic atrophy occurred in 4 patients (57.1%) whereas 3 patients (42.9%) revert back to normal.

DISCUSSION

This observational, descriptive, longitudinal study to screen ocular findings among newly diagnosed tuberculosis patients at the time of starting of ATT and compare its findings with subsequent two visits is unique in nature. There is genuine lack of evidence regarding ocular manifestations among tuberculosis patients, be it ocular tuberculosis itself or due to ethambutol induced ocular toxicity.

The male preponderance in the present study was due to the fact that men are the working population and their healthcare seeking behaviour is more than females [12]. Genome-wide linkage study suggested a linkage between regions of the chromosome X and TB which could contribute to the excess of TB in males in many populations [12]. The role of education has long been recognised in literature for health awareness as well as health seeking behaviour more so for tuberculosis like communicable diseases [13]. This higher level of illiteracy and low level of education becomes hindrance to any public health awareness program.

The largest study reported in Indian literature was conducted in 1996 on 2010 eyes of 1005 patients, with any form of tuberculosis. Overall, 1.39% patients showed ocular morbidity in this study. On the contrary the present study showed a higher proportion (7.1%) of ocular tuberculosis [14]. This higher prevalence corroborates with a study from Philippines, conducted recently among 103 pulmonary TB patients, where the prevalence was 6.8% [15]. It also corroborates with another prospective study on adult TB patients of Nigeria which reported 9.8% prevalence of ocular lesions [16]. In the present study, all the study participants having tuberculosis of any organ involvement were actively screened for ocular lesions. So, number of patients with ocular tuberculosis seems to be higher. Latest report by Government of India supports authors observations, as there has been a 12% increase in annual case notification rate of tuberculosis through RNTCP [17].

Uveal tissue involvement in tuberculosis is recognised as one of the most important sign of ocular tuberculosis. In this study, 10 out of 12 ocular TB patients had some form of uveal involvement. The exact mechanism of choroiditis in tuberculosis remains unknown. The choroiditis may be due to immune-mediated hypersensitivity reaction [3]. In this study one case had choroiditis with co-existing pulmonary tuberculosis. So, it can be assumed that this patient can have direct ocular hypersensitivity reaction to tubercular antigens leading to development of choroiditis. Significant high association of serpiginous

Subjects	Colour vision			Contrast sensitivity	Perimetry			Visual evoked potential report			Total
	Normal	Red green defect	Could not be performed	Mean score±SD	Normal	Central scotoma	Haemianopic field defect	Normal	Demyelinating and axonal type retino-optic pathway dysfunction	Gross axonal type of retino-optic pathway dysfunction	
At the time of diagnosis of suspected ethambutol toxicity	0	4 (57.1%)	3 (42.9%)	0.73±0.96	0	5 (71.4%)	2 (28.6%)	0	6 (85.7%)	1 (14.3%)	7 (100.0%)
At the completion of therapy	3 (42.9%)	0	4 (57.1%)	0.77±0.97	3 (42.9%)	0	4 (57.1%)	3 (42.9%)	3 (42.9%)	1 (14.3%)	7 (100.0%)

[Table/Fig-5]: Colour vision and contrast sensitivity, perimetry and VEP results among subjects with suspected ethambutol toxicity (n=7).

like choroiditis with tuberculosis is well documented in the literature supports this observation [18]. In this study, one patient had anterior and intermediate uveitis without any extraocular involvement clearly indicating tubercular hypersensitivity reactions, whereas, another patient had bilateral anterior and intermediate uveitis with tubercular meningitis along with occipital lobe infarction. This natural history suggests secondary dissemination of bacilli in brain and meninges subsequently to choroid giving rise to anterior and intermediate uveitis as a part of hypersensitivity reaction. It was evident from this study that chronic uveitis responds well with ATT and steroids. This finding also supports the observations of Gupta V et al., [19].

Tubercular retinal vasculitis can be result of delayed type of hypersensitivity. Two patients had Eales disease as they presented with active uniocular vitreous haemorrhage, which later on resolved with ATT and steroids. Vitreous haemorrhage can be a presenting feature of tubercular vasculitis and it resolves following treatment with ATT and steroids [20]. Recently, tubercular DNA has been detected by PCR in a vitreous fluid specimen shows the association of *M. tuberculosis* with Eales disease [21].

Choroidal tuberculoma develops from a haematogenous spread of the tubercular bacilli. So, tuberculoma is an active tubercular infection. Choroidal tubercles can be associated with tubercular meningitis or military tuberculosis. In this study one of the patients of tubercular meningitis developed multiple bilateral choroidal tubercles. Association of choroidal tubercles with meningitis is well documented in literature [22]. In this study, one patient of miliary tuberculosis also developed multiple choroidal tubercles. The association of choroidal tubercles in military tuberculosis has been documented long back by Dolfus MA and Albaugh GH [23]. They found that out of 37 cases of military tuberculosis 18 had tubercles (48.7%) and out of 29 military tuberculosis with meningitis 20 had tubercles (68.9%) [23]. Association of choroidal tuberculoma with systemic dissemination of tuberculosis further supported by a recently conducted study showing the association with disseminated TB at the rate of 2.8% in African TB patients [24].

The incidence of ethambutol-induced ocular toxicity varies widely, as reported in various literature. Among the Indian studies incidence was reported to be in the range from 0.6% to 3% [25-27]. Incidence of suspected ethambutol-induced ocular toxicity in the index study is 4.11%, where seven patients out of 170 study participants suffered from ethambutol induced ocular toxicity. In the present study, ethambutol toxicity cases have been detected early due to active screening.

Ethambutol-induced toxicity usually develops late. Though mean duration of development of toxicity is 3 to 5 months it can develop as early as 1.5 months [5]. This study findings show mean duration of detection of toxicity is 2.86 months. As active screening for antitubercular drug toxicity was carried out in this study estimated mean duration of diagnosis of suspected ethambutol toxicity seems to be shorter. This finding is consistent with the observation of Chan RY and Kwok AK [5].

The type of colour-vision abnormality induced by ethambutol has not been clearly established [28]. At the end of six months follow-up period normalisation in colour vision was noted in three out of seven patients suffering from ethambutol-induced ocular toxicity. Colour vision improvement following withdraw of ethambutol has long been recognised in literature [29].

Although all the patients had improvement in contrast sensitivity score from their score at the time of detection of ethambutol toxicity but this improvement is not statistically significant (p-value=0.854). The present study findings on Pelli-Robson contrast sensitivity does not corroborate with Kandel H et al., though Pelli-Robson test has high test-retest reliability [30]. Due to the small number of subjects that suffered from suspected ethambutol-induced ocular toxicity it is difficult to comment on contrast sensitivity test [31].

Visual field defect is one of the commonest findings of antitubercular drug induced ocular toxicity. This study supports the observations regrading reversal of visual field defects following withdraw of ethambutol [32]. Upto 80% normalisation of visual field after stoppage of ethambutol is reported in literature [29,33].

Kim LK and Park PS clearly depicted the role of VEP, especially P-100 latency, in early diagnosis of ethambutol toxicity as well as significant reduction of prolonged P-100 latency after ethambutol stoppage [34]. The present study supports this observation regarding the improvement in P-100 latency of VEP reports.

The reversibility of ethambutol toxicity has been always a debatable question as reported in literature time to time [33]. Although classically described as reversible on discontinuation of ethambutol, permanent visual impairment without recovery has also been reported [5]. In this study out of seven patients, three recovered to normalcy completely, while four developed optic atrophy. This finding of optic atrophy only signifies unpredictability of ethambutol toxicity even when recommended doses are used [35].

Antitubercular drug induced optic neuropathy can be caused by both ethambutol and isoniazid [36]. Only ethambutol was withdrawn and retrobulbar neuritis was treated as per recommended guidelines. The incomplete reversal of anti-tubercular toxicity may be due to ethambutol itself or may be due to combined effect of ethambutol and isoniazid or isoniazid alone.

Limitation(s)

Optic neuropathy is caused by both ethambutol and isoniazid. However, isoniazid-induced isolated optic neuropathy was not taken into consideration in the present study.

CONCLUSION(S)

The study observation strongly recommends conducting a baseline visual assessment to rule out existing ocular morbidity and co-existing ocular tuberculosis at the same time. Patients should be advised to contact health facility if any alteration of vision. In that case prior baseline ocular data can be compared with the new findings and ethambutol toxicity can easily be detected. Early detection of toxicity and withholding of offender can cause visual recovery. It is also necessary to do translational research to detect pathophysiology of ethambutol-induced ocular toxicity.

Acknowledgement

Authors acknowledge the co-operation of the RNTCP personnel, staffs of the Department of Pulmonary Medicine and Ophthalmology and also thank Mr. Souvik Dutta for his immense help to derive the statistical analysis for the present study.

REFERENCES

[1] Shakarchi FI. Ocular tuberculosis: Current perspectives. Clin Ophthalmol. 2015;9:2223-27.
[2] Sharma A, Thapa B, Lavaju P. Ocular tuberculosis: An update. Nepal J Ophthalmol. 2011;3(5):52-67.
[3] Kokkada SB, Barthakur R, Natarajan M, Palaian S, Chhetri AK, Mishra P. Ocular side effects of antitubercular drugs–a focus on prevention, early detection & management. Kathmandu Univ Med J (KUMJ). 2005;3(4):438-41.
[4] Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997;13:473-77.
[5] Chan RY, Kwok AK. Ocular toxicity of ethambutol. Hong Kong Med J. 2006;12(1):56-60.
[6] Lal BB, Gupta LR. Visual pattern in ethambutol treated tubercular patients. Ind J Tub. 1982;29(4):222-25.
[7] Chung KJ, Park YB, Park SP. Visual function test for early detection of ethambutol-induced ocular toxicity. Journal of the Korean Ophthalmological Society. 2012;53(5):694-699. Available at: https://synapse.koreamed.org/articles/1009359.
[8] Killer HE, Job O, Forrer A. Retrobulbar neuritis-diagnosis and differential diagnosis. Praxis (Bern 1994). 1996;85(17):554-58.
[9] Ocular TB. Index-TB guidelines. Guideline on extra-pulmonary tuberculosis for India. New Delhi: Ministry of Health & Family Welfare. Central Tuberculosis Division; [cited 2019 Aug 15]. Available from: https://tbcindia.gov.in/showfile.php?lid=3245.
[10] Technical and Operational Guidelines for TB Control in India 2016. New Delhi: Ministry of Health & Family Welfare. Central Tuberculosis Division; [cited 2021 Sep 19]. Available from: https://tbcindia.gov.in/showfile.php?lid=3219.

[11] Undrakonda V, Yashodhara BM, Gonsalves S, Shashikiran U, Kapoor S. Bilateral retrobulbar neuritis following cessation of ethambutol. Int J Case Rep Images. 2015;6(2):76-80.
[12] Neyrolles O, Quintana-Murci L. Sexual inequality in tuberculosis. PLoS Med. 2009;6(12):e1000199. Doi: 10.1371/journal.pmed.1000199.
[13] Narayan B. Tuberculosis in India: A need of public awareness & education. University of Mauritius Research Journal. 2015;21:01-27.
[14] Biswas J, Badrinath SS. Ocular morbidity inpatients with active systemic tuberculosis. Int Ophthalmol. 1995-96;19:293-98.
[15] Lara LPR, Ocampo V. Prevalence of presumed ocular tuberculosis among pulmonary tuberculosis patients in a tertiary hospital in the Philippines. J Ophthalmic Inflamm Infect. 2013;3:1.
[16] Egbagbe EE, Omoti AE. Ocular disorders in adult patients with tuberculosis in a tertiary care hospital in Nigeria. Middle East Afr J Ophthalmol. 2008;15(2):73-76.
[17] TB surveillance and epidemiology. India TB report 2020. New Delhi: Ministry of Health & Family Welfare. Central Tuberculosis Division; [cited 2021 Aug 15]. Available from: https://www.tbcindia.gov.in/showfile.php?lid=3538.
[18] Wiehler U, Mackensen F, Max R, Dalpke A, Zimmermann S, Becker M. Tuberculosis: An underestimated cause of serpiginous choroiditis? Investigative Ophthalmology & Visual Science. 2007;48:348.
[19] Gupta V, Gupta A, Rao NA. Intraocular tuberculosis-an update. Surv Ophthalmol. 2007;52(6):561-87.
[20] Patricio MS, Portelinha J, Passarinho MP, Guedes ME. Tubercular retinal vasculitis. BMJ Case Rep. 2013;2013:bcr2013008924.
[21] Madhavan HN, Therese KL, Doraiswamy K. Further investigations on the association of Mycobacterium tuberculosis with Eales' disease. Indian J Ophthalmol. 2002;50:35-39.
[22] Mehta S, Chauhan V, Hastak S, Jiandani P, Dalal P. Choroidal tubercles in neurotuberculosis: Prevalence and significance. Ocul Immunol Inflamm. 2006;14(6):341-45.
[23] Dolfus MA, Albaugh GH. Fundus lesions in tuberculous meningitis and miliary pulmonary tuberculosis treated with streptomycin. Am J Ophthalmol. 1949;32:821-24.
[24] Beare NA, Kublin JG, Lewis DK, Schijffelen MJ, Peters RP, Joaki G, et al. Ocular disease in patients with tuberculosis and HIV presenting with fever in Africa. Br J Ophthalmol. 2002;86:1076-79.
[25] Tiwari US, Mishra BP. Ocular toxicity of ethambutol: A clinical study. Lung India. 1987;3:111-13.
[26] Sharma GS, Purohit SD, Lodha SC. Comparative study of isoniazid and ethambutol with isoniazid ethambutol and pyrazinamide in the retreatment of pulmonary tuberculosis. Ind Med Gaz. 1975;15:140.
[27] Narang RK, Varma B. Ocular toxicity of Ethambutol (A clinical study). Indian J Ophthalmol. 1979;27:37-40.
[28] Emerson CM, Frances PG, Karlo ALP, Evelyn SMT, Ma NRL. Colour-vision abnormalities among patients undergoing tuberculosis treatment. Philipp J Ophthalmol. 2010;35(1):03-09.
[29] Schild S Harris, Fox C Barry. Rapid-onset reversible ocular toxicity from ethambutol therapy. Am J Med. 1991;90(3):404-06.
[30] Kandel H, Adhikari P, Shrestha GS, Ruokonen EL, Shah DN. Visual function in patients on ethambutol therapy for tuberculosis. J Ocul Pharmacol Ther. 2012;28(2):174-78.
[31] Elliott BD, Sanderson K, Conkey A. The reliability of the Pelli-Robson contrast sensitivity chart. Ophthalmic Physiol Opt. 1990;10(1):21-24.
[32] Mahrukh, Ashraf A, Bhat A Md. Visual field changes in patients receiving antitubercular drug therapy at tertiary care hospital: An analytical observational study. International Journal of Contemporary Medical Research. 2017;4(2):346-49.
[33] Goyal JL, De Sarmi, Singh NP, Bhatia A. Evaluation of visual functions in patients on ethambutol therapy for tuberculosis: A prospective study. J Commun Dis. 2003;35(4):230-43.
[34] Kim LK, Park PS. Visual function test for early detection of ethambutol induced ocular toxicity at the subclinical level. Cutan Ocul Toxicol. 2016;35(3):228-32.
[35] Sobota I, Czik T. Vision impairment in the course of lung tuberculosis treatment. [Article in Croatian] Acta Med Croatica. 2006;60(2):181-84.
[36] Rodriguez-Marco NA, Solanas-Alava S, Ascaso FJ, Martinez-Martinez L, Ru-bio-Obanos MT, Andonequi-Navarro J. Severe and reversible optic neuropathy by ethambutol and isoniazid. An Sist Sanit Navar. 2014;37(2):287-91.

PARTICULARS OF CONTRIBUTORS:
1. RMO cum Clinical Tutor, Department of Ophthalmology, Bankura Sammilani Medical College, Bankura, West Bengal, India.
2. Associate Professor, Department of Pulmonary Medicine, Burdwan Medical College, Purba, Burdwan, West Bengal, India.
3. Senior Resident cum Contractual Medical Officer, Department of Ophthalmology, B.N. Bose SD Hospital, Barrackpure, West Bengal, India.
4. Assistant Professor, Department of Medicine, Burdwan Medical College, Purba, Burdwan, West Bengal, India.
5. Professor and Head, Department of Ophthalmology, Burdwan Medical College, Purba, Burdwan, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Uttam Biswas,
1680, Madurdaha, Kolkata-700107, West Bengal, India.
E-mail: druttambiswas@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 20, 2021
- Manual Googling: Nov 06, 2021
- iThenticate Software: Nov 26, 2021 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: This study was conducted with the financial assistance from Indian Council of Medical Research (ICMR)
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 18, 2021**
Date of Peer Review: **Sep 14, 2021**
Date of Acceptance: **Nov 08, 2021**
Date of Publishing: **Dec 01, 2021**