International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Ocular Manifestations in Cat IV Eligible and XDR Pulmonary and Extra Pulmonary Tuberculosis Patients in Government DOT Plus Centre

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Abstract: ***Background: The prevalence and the patterns of ocular tuberculosis (TB) are largely undocumented among Multidrug Resistant TB (MDR-TB) and Extensive drug resistance TB(XDR TB) patients. Method: A prospective study was conducted at department of Ophthalmology, NCH Surat from January 2015 to November 2016. Patients with established diagnosis of MDR and XDR, both pulmonary and extrapulmonary TB were recruited from the TB DOTS programme. Complete ocular examination including best corrected visual acuity (BCVA), colour vision, anterior segment and dilated posterior segment examination was carried out on all patients before starting treatment. These patients were followed monthly for first 6 months and then at twelfth month of diagnosis. The diagnosis of presumed ocular tuberculosis was made when clinical signs of tuberculosis (TB) uveitis were found in the participants. Result: Seven (3.57%) out of total 187 patients included in study showed signs of presumed ocular tuberculosis. There was no age, sex predilection between those who had presumed ocular TB and those who had not. Colour vision was defective in 2(1.07%) patients, anterior uveitis was found in 1(0.53%)patient, choroiditis in 1(0.53%)patient, multifocal choroiditis in 1(0.53%)patient, Eale's disease in 1(0.53%)patient, serpiginous choroiditis in 1(0.53%)patient, choroidal tubercle in 2(1.07%)patients. Conclusions: Presumed ocular tuberculosis should be considered in MDR and XDR, both pulmonary and extrapulmonary TB patients. Common ocular lesion found in the study was choroidal tubercle.***

Keywords: Choroidal tubercle, Drug resistant TB, Uveitis, extra pulmonary TB

1. Introduction

Tuberculosis (TB) is a multisystem infectious disease caused by *Mycobacterium tuberculosis(MTB).* According to the World Health Organization, approximately one-third of the world's population are infected by TB; 10% of infected people are symptomatic and 90% have latent TB [1,2]

A major obstacle to TB control is the emergence of mycobacterial resistance to anti-tuberculous chemotherapy [3]. Anti-tuberculosis drugs are a two-edged sword. While they destroy pathogenic M. tuberculosis they also select for drug resistant bacteria against which those drugs are then ineffective. Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to both isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with additional resistance to any fluoroquinolone and to at least one of three injectable second-line anti-tuberculosis drugs used in treatment (capreomycin, kanamycin or amikacin). It is to be noted that Rifampicin resistance is quite rare without isoniazid resistance. The great majority of DST results with rifampicin resistance will also be isoniazid resistance, i.e. MDR TB. Therefore RNTCP has taken the programmatic decision that patients who have any Rifampicin resistance, should also be managed as if they are an MDR TB case. These patients are labelled as CAT IV eligibleTB. More cases of drug resistant TB have come to surface owing to improved diagnostics and upgraded healthcare infrastructure in recent years. It is estimated the prevalence of MDR-TB to be about 3% in new cases and 12-17% in re-treatment cases. An estimated 9.7% of people with MDR-TB have XDR-TB. The latest WHO global resistance report, released in Oct. 2013, estimated that there were 79,000 cases of MDR-TB from India in 2012[4]. This accounted for 17.6% of the world's MDR-TB burden. Ocular tuberculosis results from the haematogenous dissemination of mycobacteria and may affect virtually any intraocular tissue. Clinical features depend on the specific tissue involved and may be due to both, direct tissue infection or due to hypersensitivity reactions. The characteristic findings include tubercles, tuberculomas and serpiginous-like choroiditis. These represent direct choroidal infection via the hematogenous route. Less common lesions include lupus vulgaris of the eyelids, conjunctivitis, corneal ulcers and phlyctenulosis, and scleritis. Neuroopthalmological lesions include orbital apex syndrome, disc edema and sixth nerve palsies. Non-invasive ocular examinations to detect ocular tuberculosis have several potential advantages. They may suggest a diagnosis in a subset of patients, thus allowing for a more focused investigational approach. The association between systemic TB disease and ocular dissemination has been widely reported. The ocular morbidity pattern in 2010 eyes of 1005 patients with active pulmonary and extrapulmonary tuberculosis disease was studied prospectively in India; 1.4% of patients had ocular lesions [4]. In a study from Spain, Bouza et al. examined 100 patients with culture-positive tuberculosis and found that 18 (18%) of patients had tubercular choroiditis, papillitis, retinitis, and vitritis [5]. Systemic dissemination has also been reported to significantly increase the likelihood of ocular lesions up to 60% [6]. It is unclear whether the dual HIV-TB epidemic has lead to an increase in the prevalence and incidence of ocular tuberculosis in patients with active TB disease and co-infected with HIV. In various studies from Africa, differing proportions of ocular tuberculosis in association with HIV infection have been reported, varying between 0 to 2.8%, depending on the size and clinical characteristic of the studied cohort [6,7]. In a prospective study from Mumbai, India, 23.5% of AIDS patients with systemic tuberculosis had ocular lesions [8] but a much lower prevalence was seen in a neighbouring city, where although as many as 66% of 1268 AIDS patients had systemic tuberculosis, only 1% of patients had ocular TB [9]. Babu et al., in the largest Indian

cohort of referred HIV/AIDS patients (766) from a tertiary care centre, described ocular tuberculosis in 19 eyes of 15 patients (2.0%). Clinical presentations included choroidal granulomas in 10 eyes, subretinal abscess in seven eyes (worsening to panophthalmitis in three eyes), and conjunctival tuberculosis and panophthalmitis each in one eye [8]. To-date, no data are available on the overall prevalence or common presentations of ocular tuberculosis, in patients with MDR-TB. The objectives of this study were 1) To assess incidence of ocular manifestations associated with CAT IV Eligible TB (MDR TB) & XDR TB patient during study period. 2)To assess spectrum of ocular manifestations associated with MDR & XDR TB.

2. Results

In this study 187 patients were examined, mean age was 30.5 (± 12.55) years, 112 males (60%) and 75 females (40%), 180 (96.26%) patients had pulmonary tuberculosis and 7 (3.74%) had extrapulmonary tuberculosis, 171(91.44%) had MDR TB and 16(8.56%) had XDR TB. Incidence of ocular TB in MDR-TB AND XDR-TB was 3.74% (seven patients). It was more common in 20-39 years of age group (3.20%), 4(2.14%) male and 3(1.60%) female patients were affected which is not statistically significant (p value 0.8090). 2 patients had visual acuity 6/6 to 6/18, 2 patients had <6/18 to 6/60, 2 patients had <6/60 to 3/60 and 1 patient had <3/60 to 1/60 at the time of manifestation of ocular disease and at at twelfth month's 5 patients had visual acuity between 6/6 to 6/18, 1 patient had <6/18 to 6/60, 1 patient had <6/60 to 3/60. Out of seven patients, 5 patients had vision 6/60 or more at twelfth month, 1 patient had vision <6/60. Posterior segment findings present 6 (85.71%) patients and anterior segment findings in 1(14.29%)patient .Choroidal tubercle was most common ocular manifestation. Others were serpigonous choroiditis, anterior uveitis, choroiditis, multifocal choroiditis, and Eales disease. 5(2.67%) affected patients had pulmonary TB and 2(1.07%) had Extrapulmonary TB which was statistically significant (p value 0.02422).Amongst affected, 6(3.21%)patients had MDR TB and 1(0.53%)patient had XDR TB which is statistically not significant (p value 0.8916).

3. Discussion

In this study, 187 patients were examined, majority of the patients belonged to 20-39yrs which constitutes the working population and are exposed to outdoor activities and thus increased risk of transmission of tuberculosis. Salil Mehta et al study, 47 MDR/HIV co infected patients were examined. Age ranged from 12 years to 54 years (mean 39 years, SD: 8.7). Biswas J et al study, 1005 patients were examined prospectively in South India. E.E. Egbagbe et al study, 92 patients were examined with mean age 37.9 years. In present study, male are more commonly affected i.e. 112 male patients (60%) and 75 females (40%). There is no statistically significance in gender distribution (p value 0.2067). Salil Mehta et al study, there was 28 (59.6%) males, 17(36.2%) females and two (4.2%) transgender. E.E. Egbagbe, et al study, there were 45(48.91%) males and 47(51.08%) females. In India male is the working and dominant member of the family hence involved more in outdoor and extracurricular activities whereas females are ignored portion of the society and are deprived of the health care, and this may be the reason for less reporting of female patients in health care system.

In this study, 180 (96.26%) patients had pulmonary tuberculosis and 7 (3.74%) had extrapulmonary tuberculosis. Salil Mehta et al study, 14 (24.8%) had extrapulmonary TB (EPTB).

India is a developing country with major population from low socioeconomic class living in overcrowded areas with poor ventillation thus favouring inhalation and transmission of tubercle bacilli thus the increased prevalence of pulmonary TB.

In present study 171(91.44%) patients had MDR TB and 16(8.56%) patients had XDR TB. Salil Mehta et al study, 44 patients (93.6%) had MDR, and three patients (6.6%) had XDR.

Majority of the tubercle bacilli are resistant to Isoniazid and Rifampicin but are still susceptible to Flouroquinolones and second line of Anti-tuberculosis drugs and thus more MDR TB patients.

In our study, the incidence of ocular TB in MDR-TB AND XDR-TB was found to be 3.74%. Biswas et al, Mehta, E.E.Egbagbe, Leon Paolo R Lara et al study, percentage ocular manifestations amongst TB patient was 1.39%, 3%, 9.80%, and 6.80% respectively.

Table 1: Percentage of TB patients showing ocular manifestations in various studies

Year	*Country*	*Author*	*Percentage of TB Patients with Ocular Manifestations*
1996	India	Biswas et al	1.39%
2004	India	Mehta	3%
2008	Nigeria	E.E.Egbagbe	9.80%
2013	Philippines	Leon Paolo R Lara et al	6.80%

Bouza et al, Beare et al, Mehta and Gilada et al study, percentage of ocular manifestations amongst TB patients coinfected with HIV was 18%, 2.02% and 23.50%.

Table 2: Percentage of TB patients coinfected with HIV showing ocular manifestations in various studies

Year	Country	Author	Percentage of TB + HIV Patients with Ocular Manifestations
1997	Spain	Bouza et al	18%
2002	Africa	Beare et al	2.02%
2005	India	Mehta and Gilada	23.50%

Mehta et al study ocular manifestations were present in 12.07% patients coinfected with HIV AND MDR TB while in our study of MDR AND XDR TB it was 3.74%.

Table 3: Comparison of percentage of MDR TB patients showing ocular manifestations with other study

Year	Country	HIV Status	Author	Percentage of MDR TB Patients with Ocular Manifestations
2013	India	Positive	Mehta et al	12.07%
2016	India	Negative	Present study	3.74%

When a patient has both HIV and TB, each disease speeds up the progress of the other. In addition to HIV infection speeding up the progression from latent to active TB, TB bacteria also accelerate the progress of HIV infection. An estimated prevalence of HIV infection amongst TB patients is around 13%. Our study reveals a higher incidence of ocular manifestations than that reported by Biswas et al. in a cohort of pulmonary tuberculosis patients in an era where drug resistance was presumably far less common, but less than that reported by Mehta et al. in a cohort of HIV/TB patients. Both these reports and other similar studies did not address the issue of drug resistance in enrolled patients and this remains an unknown factor that does not permit accurate comparisons and cross match these studies. It is possible that an increasing prevalence of drug-resistant tuberculosis, with or without HIV infection, is causing a corresponding increase in the incidence of ocular manifestations amongst tuberculosis patients. Overall visual acuity was better at 12^{th} months of treatment signifying early diagnosis and timely intervention may improve ocular morbidity.

In our study, posterior segment(85.71%) of eye affected more than anterior segment. In Mehta et al 2013 study, anterior segment examination was normal in 96% patients of MDR/HIV coinfection and seven (15.5%) patients were showed posterior segment findings. The most common mode of infection of ocular tissue in systemic tuberculosis is hematogenous spread. Choroid is most commonly affected because of its high blood supply. This may be responsible for higher posterior segment involvement in systemic tuberculosis.

Table 4: Ocular manifestations in MDR and XDR TB patients

Ocular Manifestations in MDR and XDR TB Patients		No. of Patients
Anterior Segment Findings	Anterior Uveitis	1
Posterior Segment Findings	Choroiditis	1
	Multifocal choroiditis	1
	Eales disease	1
	Choroidal tubercle	2
	Serpiginous like choroiditis	1
Total		**7**

Biswas J, et al study, the most common ocular finding was bilateral healed focal choroiditis (50%). No case of Eales' disease was found in this series. Bouza E, et al study, almost all patients (17/18) had choroiditis,and other ocular lesions included papillitis, retinitis, vitritis, vasculitis, dacryoadenitis, and scleritis. Salil Mehta study, five of the six patients had choroidal tubercles and one had retinal vasculitis. N A V Beare, et al study, in Malawian patients with TB presenting acutely with fever, choroidal granulomas were found in 2.8% patients with mycobacteraemia and AIDS. Mehta S, et al study, ocular lesions included tubercles (1 eye of 3 patients) and chorioretinitis (1 eye of 1 patient). Babu RB, et al study, presentations of ocular TB included choroidal granulomas in 10 eyes(52.63%), subretinal abscess in seven eyes (36.84%), worsening to panophthalmitis in three eyes, conjunctival tuberculosis, and panophthalmitis each in one eye (5.26%). Salil Mehta, et al study, overall, examination of the anterior segments was normal in 45/47 patients (96%). A dilated fundus examination revealed active ocular inflammatory disease in seven eyes of seven patients (15.5%). 'These included five eyes of five patients (10%) with choroidal tubercles, one eye of one patient (2%) with presumed tubercular chorioretinitis and one eye of one patient (2%) with evidence of presumed active CMV retinitis. Presumed ocular tuberculosis was thus seen in a total of six patients (12.7%).

In present study, 5(2.67%) patients with MDR and XDR TB patients with ocular manifestations had pulmonary TB and 2(1.07%) patient had extrapulmonary TB. Ocular manifestations amongst extrapulmonary MDR and XDR TB patients were higher than pulmonary type which was statistically significant (p value 0.02422) The widespread dissemination of mycobacterial infection, which is often seen in patients with extrapulmonary tuberculosis, may explain higher ocular manifestations amongst MDR and XDR TB patients. Mehta et al 2013 study showed extrapulmonary TB is independent risk factor for ocular manifestations amongst MDR/HIV coinfected patients.

4. Conclusion

Ocular tuberculosis was seen in 3.74% patients. It was seen in economically and socially more productive age group but with timely interventions blinding complications in these patients were avoided which would otherwise further aggravate the problem. Multi drug resistance tuberculosis is emerging as a growing threat to TB control in India. Ocular manifestations in such patients are poorly studied. Present study represents various ocular manifestations in MDR and XDR TB patients. The study helps to describe spectrum of manifestations to create awareness amongst ophthalmologists and chest physician for early recognition and timely intervention to prevent blinding complications. RNTCP guideline does not include ophthalmic evaluation before start of anti tuberculosis drugs. So we strongly recommend baseline ophthalmic evaluation before initiation of treatment and then follow up evaluation six monthly.

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