ORIGINAL RESEARCH PAPER

Volume-7 | Issue-6 | June-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# PATTERN OF UVEITIS IN PATIENTS WITH VARIOUS TYPES OF SYSTEMIC TUBERCULOSIS

Ophthalmology

**Prof. Radha Annamalai** Professor of Ophthalmology, Department of Ophthalmology, Sri Ramachandra University, Porur, Chennai- 600116

**Dr. Nitin Ramanujam*** Post graduate - M .S. Ophthalmology, Department of Ophthalmology, Sri Ramachandra University, Porur, Chennai- 600116 *Corresponding Author

**Prof. Dr. M. Muthayya** Professor of Ophthalmology, Department of Ophthalmology, Sri Ramachandra University, Porur, Chennai- 600116

## ABSTRACT

**Introduction:** Tubercular uveitis is a frequent cause of visual morbidity. Ocular inflammation can have rapid dissemination and result in anterior, intermediate, posterior or panuveitis.

**Materials and methods:** This is a prospective study on 125 patients over three years. Patients with tuberculosis were evaluated for uveitis at a Uveitis clinic at Sri Ramachandra University, Chennai. Angiography, complete blood count, X-ray, polymerase chain reaction and biopsy were performed on blood, aqueous and vitreous. Treatment was with ATT.

**Results:** Among 125 patients, Uveitis was present in 12% and posterior type was the most common with $p < 0.05$. Manifestation was earliest in miliary and pulmonary tuberculosis. Active disease had more severe uveitis than latent TB. Response to ATT was seen in 93%.

**Conclusion** – Uveitis due to TB can occur in pulmonary and extrapulmonary TB. Ophthalmic evaluation of both latent and active TB can prevent visual loss.

## KEYWORDS

uveitis, tuberculosis, choroiditis

### Introduction

Tuberculosis (TB) continues to remain a health concern in both developing and developed countries. Despite advances in investigative modalities and well defined treatment regimens, tubercular uveitis (TU) is a diagnostic and therapeutic challenge. This is because of the variation in presentation, nature of the tubercle bacilli and its ability to involve any organ in the body. Visual loss in TB can occur due to involvement of the eyelids, orbit, cornea, uvea, vitreous, retina or optic nerve. Haematogenous dissemination of the tubercle bacilli results in ocular inflammation and the uveal tract is the most frequently affected because of its rich vascular supply. Uveitis in TB could be due to direct infection or due to immune mediated hypersensitive reaction to the tubercle bacilli[1].

In latent tuberculosis where no active infection can be detected there is may be no lesion but the DNA of the bacillus can still be detected. Risk factors for TB include HIV infection and other causes of immunosuppression such as pregnancy, treatment with corticosteroid or immunosuppressive agents. In a recent study from Cambodia, done on 450 HIV-infected persons who completed TB screening, TB was diagnosed in 24%[2].

Clinical manifestations of uveitis in TB can be acute anterior uveitis, chronic granulomatous anterior uveitis, intermediate uveitis, vitritis, uveitic macular oedema, retinal vasculitis, focal or multifocal choroiditis, subretinal abscess, endophthalmitis, neuroretinitis and panophthalmitis.

The incidence of TU varies between different populations and races. It would also depend on the endemicity of the systemic disease and high endemic areas have more severe and frequent uveitis. The incidence reported by various authors is summarised in the following table[3]:

**Table 1: Incidence of TB uveitis in various ethnic races**

| | |
|---|---|
| 16% | Saudi Arabia |
| 18% (culture-proven) | Spain |
| 2.8% (among HIV-positive TB) | Africa |
| 10.5% of all cases of uveitis | High endemic area of TB |
| 6–7% of all uveitis | Low endemic area of TB. |

Significant advances have been made in the investigation of TB uveitis. A thorough clinical examination needs to be followed by both ancillary and laboratory tests in all patients. Microbiological workup may be difficult due to the paucity of ocular sample. Biopsy and histopathological examination are done if laboratory tests are negative but clinical suspicion remains high. A diagnosis of TB is made if specimens shows caseating granuloma or if acid fast bacilli are detected using Ziehl-Neelson staining. A study performed by Biswas and associates on 1,005 patients from South India with active pulmonary and extrapulmonary tuberculosis reported ocular morbidity of 1.39% in these patients[4].

A differential diagnosis of other causes of uveitis needs to be considered as they can present with similar features. Infections such as syphilis or toxoplasmosis and non-infectious etiologies such as sarcoidosis or Vogt Koyanagi Harada syndrome need to be ruled out before starting the patient on anti-tubercular treatment (ATT). Although TB is endemic in India, management of TB is guided by a combination of thorough clinical evaluation, relevant investigations and meticulous follow-up after ruling out autoimmune and non-infectious causes.

### Materials and methods

This is a prospective observational study, performed on 125 patients over a period of 3 years at Sri Ramachandra University, Chennai, India, a multispecialty tertiary medical centre. Institutional ethics committee approval was obtained and the study was conducted after informed consent was got from the patients. This study was performed in concurrence with the departments of internal medicine, respiratory medicine, TB and chest clinic. Their opinions were sought for systemic clinical evaluation and management. All patients who presented with ocular complaints such as defective vision, pain, congestion, photophobia and watering were referred to the ophthalmology clinic and a routine uveitis workup was performed on them.

Patients were considered eligible and included in the study if there was an ocular complaint with a past history of TB, clinical suspicion, systemic microbiological tests had proven TB or if the patient was on treatment with ATT. Patients with no ocular complaints, no evidence of uveitis, or had no systemic TB were excluded from the study. Data collection was performed and all relevant information on race, ethnic origin, contact with TB, previous similar illness and history of past and present immune status were obtained.

Systemic investigations included complete blood count, Erythrocyte Sedimentation Rate (ESR), C-reactive protein, Polymerase chain

reaction (PCR), QuantiFERON (QFT) TB Gold test, Mantoux test, Chest X-Ray or Computed Tomography (CT) of chest and was done on all patients. Additional blood, ultrasound and radiological investigations were done as advised by the treating physician. Ocular investigations performed included fundus photography, fundus fluorescein angiography (FFA), indocyanine green angiography (ICG), B scan ultrasonography and optical coherence tomography (OCT). Microbiological assay in the laboratory was done using PCR and real time PCR (RT- PCR) on both blood and ocular tissue. Ocular samples used for analysis were aqueous, vitreous or rarely chorioretinal tissue [5].

Treatment of patients with indeterminate results was based on discretion. Patients were considered positive for TB and treatment started immediately if PCR, RT- PCR or QFT on blood, anterior chamber fluid or vitreous was positive, if systemic investigations were positive or if clinical features were highly suggestive of TB. ATT for 9 months was the standard treatment for most patients of which isoniazid (INH), rifampicin, ethambutol and pyrazinamide was given for 5 months followed by isoniazid and rifampicin for 4 months [6].

Shorter duration of ATT was based on resolution of signs, clinical response in terms of visual improvement and systemic status. Oral corticosteroids were given when indicated as in patients with subretinal abscess. Topical corticosteroids and cycloplegic agents were administered for patients with anterior uveitis. Surgery was required in some patients for secondary glaucoma and retinal detachment. Management for all patients was done only after consultation with the physician and infectious disease specialist.

For both clinical evaluation prior to starting treatment and to judge response, Standardization of Uveitis Nomenclature (SUN), Working Group Classification [7] was used. Visual acuity was assessed using Snellen chart and comparison was done before and after treatment.

Follow up was done at the uvea clinic and internal medicine department and depended on individual patient progression and response. During each review, ocular complications such as complicated cataract, post inflammatory glaucoma, macular scarring, choroidal neovascular membranes, retinal detachment, cystoid macular oedema and neovascularisation were looked for and if present treated. We also monitored for the side effects of ATT such as decreased visual acuity, central scotoma, colour vision defects and optic neuritis which are commonest with ethambutol toxicity. INH is known to cause idiopathic intracranial hypertension and hence colour vision testing, visual field examination using automated perimetry and a thorough fundus examination was done at regular intervals. Statistical analysis was performed using chi square test and SPSS software. Results were considered as statistically significant if $p < 0.05$.

**Aim**

The aim of this study was to identify the incidence of tubercular uveitis, type of inflammation, the most common type of TB and cause of visual loss in tubercular uveitis.

The secondary objective was to identify the type of systemic and ocular investigations which would be useful as a diagnostic modality and to assess the response to ATT.

**Results**

125 patients with active TB or history of TB were referred to the uvea clinic for screening for uveitis over a 3 year period and the minimum period of follow up of patients was 9 months. Evaluation showed that 36 (12%) patients had tubercular uveitis in various forms. This incidence was found to be statistically significant with $p = 0.03$. There were 34 (65%) males and 17 (33%) males between the ages 20 to 60 years and a mean age of 40 (SD +/- 15). Predominant involvement was noted in the 3rd and 4th decades of life. Bilateral ocular presentation was present in 18% of patients and was commonly due to iridocyclitis. 41 patients had ocular complaints, the most common of which was defective vision, floaters and pain. 21 patients had acute loss of vision due to involvement of the macula. The other less common symptoms were redness, watering and visual field defects. Among 36 patients, 21(58%) had active TB and 15 (42%) patients had latent TB. Pulmonary TB was present in 12(57%) and extrapulmonary TB in 9 (42%) of patients. Among those with extrapulmonary TB, 1 patient (8%) had abdominal TB, 6(50%) had miliary TB, 3(25%) had TB of the central nervous system and 2(16%) had spinal TB.

**Table 2: Type of Tuberculosis causing Tubercular Uveitis**

| | |
|---|---|
| Active Tuberculosis | 21(58%) |
| Latent Tuberculosis | 15(42%) |
| Pulmonary Tuberculosis | 12(57%) |
| Extrapulmonary Tuberculosis | 9(42%) |

Anterior uveitis was present in 19%, intermediate uveitis in 11%, posterior uveitis in 61% and panuveitis in 9%. The nature of uveitis was acute in 18 and chronic in 33 patients. At presentation, clinical features noted were granulomatous iridocyclitis in 8 (15%), intermediate uveitis in 12 (23%), focal choroiditis in 5 (10%), subretinal abscess in 3(6%), multifocal (figure 1) or serpiginous like choroiditis in 16 (31%) and vasculitis (figure 2) in 7 (14%) patients. Response to ATT was seen at the end of 2 months in the majority of patients but complications developed in 12 (23%) of them. Ocular features were reversible in 42 patients (82%) with treatment and blinding irreversible complications caused loss of vision in 9 (18%) of our patients.

**Table 3: Ocular Feature in TB Uveitis**

| | |
|---|---|
| Multifocal Choroiditis | 16(31%) |
| Intermediate Uveitis | 12(23%) |
| Iridocyclitis | 8(15%) |
| Vasculitis | 7(14%) |
| Focal Choroiditis | 5(10%) |
| Subretinal Asbcess | 3(6%) |

Lymphocytois and elevated ESR were seen in 88% and chest x ray was abnormal in 41%. Radiographic features seen in our study patients were apical cavitation, consolidation with hilar lymphadenopathy and nodular infiltrates and were consistent with active pulmonary TB. CT was used to confirm TB in 7 patients whose chest x ray was negative. 38 patients had 10 mm or more induration following Mantoux skin test. The blood sample was positive by QFT test in 16 (31%) and by PCR in 18 (35%). Analysis of ocular fluids showed positive PCR in 9 (17%), and positive RT-PCR in 5 (9%). FFA, ICG and OCT confirmed our diagnosis and helped detect complications in 18 (35%) of patients and can be contributory tests to evaluate the response to treatment.

All patients in our study who had positive microbiological results with active uveitis were treated with ATT for 9 months. 4 drug regimen for the initial 4 months followed by 2 drugs for 5 months. Oral steroids were added in patients with subretinal abscess and recalcitrant vasculitis. 3 patients with choroiditis required immunosuppressive agents (azathioprine 100mg tapered to 50 mg over 1 year). On completion of treatment, resolution of signs and an improvement of vision was noted in 41%. The main causes of defective vision after treatment were cataract in 21%, retinal pigment epithelium atrophy in 7% and maculopathy in 4% and optic atrophy in 1% of patients. Patients were monitored at regular intervals for signs of toxicity of ATT such as retrobulbar neuritis. Thorough slit lamp and fundus examination, visual acuity, visual fields and colour vision were checked during each review and 1 of our patients developed optic atrophy post ATT.

Recurrence was noted in 6(11%) and iridocyclitis was the commonest cause for chronic relapsing uveitis. The final evaluation after completion of ATT showed improvement of vision in 43 patients (84%) and deterioration in 3 patients.

**Discussion**

This study conducted on our patients showed that TB is a significant cause of uveitis. Latent TB refers to a situation where the TB bacilli live in the host without causing symptoms. There is an immune response to the DNA of TB bacilli which have been dormant after a previously acquired infection. In such patients, a Mantoux test and QFT results may not be positive and cannot be taken as markers even if negative. Initiating treatment with ATT is guided by clinical evaluation. Detection of acid fast TB bacilli by smear, culture and nucleic acid amplification techniques are the only direct confirmatory tests of active infection which could be the cause of uveitis 8.

Again, the sensitivity of any test could render it inconclusive if it is of low sensitivity. Development of newer and more sensitive techniques of investigation for ocular TB would help in more prompt identification and timely treatment. Microbiological analysis of ocular

samples to diagnose TB uveitis is at times difficult either because of smaller number of microorganisms or lodging of bacilli in the retinal pigment epithelium (RPE) 9. Contact with active TB patient, latent TB, radiographic abnormalities and RT- PCR10 were associated with tuberculous uveitis. ESR, CRP, blood count and positive ocular findings in isolation could not predict the presence of TB as an etiology for the uveitis.

The clinical presentation is not specific and various types of manifestations which can resemble non tubercular etiology can be seen in TB uveitis. In patients with uveitis due to latent TB, PCR or culture on ocular fluids can be negative and other investigations may not be positive. It has been reported that Mantoux test was positive in 59% and chest x ray was positive in 57% of patients 11.

We found in our study that it is not clear if TBU is more frequent in active or latent TB as our data did not show any significant difference in the incidence. However, studies have shown that the association of TB uveitis with latent TB is higher. A diagnostic dilemma can cause a delay in starting treatment. Ang et al calculated positive and negative predictive values (ppv and npv) in patients with latent TB. They defined a positive value as a positive QFT or Mantoux test and a ppv of 84.6% and npv of 78.9% which was found based on response to ATT.

Chest X-Ray, TST and QFT 12 will have to be done for all patients in the initial visit as it will influence the decision on starting ATT. Among 36 patients with TB uveitis in our study population, 27 were started on ATT. They were followed up during each visit by the infectious disease specialist. ATT controls the infection and corticosteroids limit the destructive inflammatory response which occurs due to delayed hypersensitivity.

In patients with negative results despite extensive investigations, a history of contact with TB has to be considered as a cause of uveitis as the systemic disease could still be evolving and not symptomatic as yet. Complications and non-resolving inflammation were seen in 5 of our patients resulting in secondary glaucoma, cataract and uveitic macular oedema all of which caused visual loss. Besides, ATT can cause complications which usually present 3-months after treatment.

In our study, we found that patients with miliary TB and pulmonary TB had significant association with posterior uveitis. The presentation of ocular inflammation and uveitis was earliest with pulmonary TB but extensive choroiditis with macular involvement and visual loss was seen in military TB. Complete resolution of lesions with restoration of vision is seen with prompt treatment with ATT in all forms of TB. However without treatment, chronicity and complications of uveitis can develop.

Our study underlines the need for a standardized diagnostic workup and decision-making with regard to treatment with ATT. A possible difficulty with decision making could occur when uveitis of unknown etiology remains after thorough investigation. These patients should be questioned about possible TB contact. Screening blood tests could be omitted, and TST or QFT and chest radiology should be performed. After collecting this information and test results, the decision to start ATT can be standardized. Further research should focus on the additional value of systemic corticosteroids with ATT, or even treatment with corticosteroids alone.

## Conclusion

Tubercular uveitis can cause significant visual morbidity and even blindness if not detected. A negative test for systemic disease or absence of active TB does not rule out ocular involvement. A differential diagnosis of other infectious diseases such as toxoplasmosis, toxocariasis or herpetic retinitis and autoimmune disease such as sarcoidosis have to be considered before starting ATT. Analysis of intraocular fluids and biopsy of ocular tissue would be required to make a definitive diagnosis in doubtful patients. However, tubercular uveitis is associated with good prognosis if the inflammation is detected early, treated promptly and regularly followed up to avoid complications and to improve visual potential.

**Figure 1: Tubercular multifocal choroiditis**

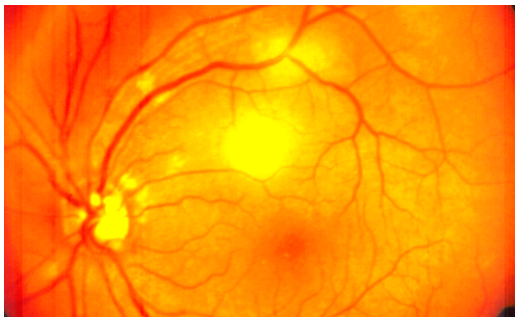
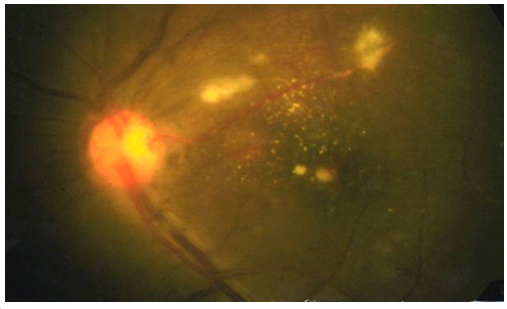


**Figure 2: Retinal vasculitis due to TB**



## References


1. Dannenberg, A.M. Delayed-type hypersensitivity and cell-mediated immunity in the pathogenesis of tuberculosis. Immunol Today. 1991; 12: 28–33
2. Centers for Disease Control and Prevention. Screening HIV-infected persons for tuberculosis-Cambodia, January 2004–February 2005. MMWR Morb Mortal Wkly Rep. 2005; 54: 1177–1180
3. V. Gupta, A. Gupta, N.A. Rao Intraocular tuberculosis—an update. Surv Ophthalmol, 2007; 52 : 561-587
4. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. Int Ophthalmol. 1995- 6; 19: 293-8.
5. Testing ocular fluids in uveitis. Bodaghi B, LeHoang P.Ophthalmol Clin North Am. 2002 Sep; 15(3):271-9
6. A.M. Abu El-Asrar, M. Abouammoh, H.S. Al-Mezaine. Tuberculous uveitis. Middle East Afr J Ophthalmol. 2009; 16: 188-201
7. Yeh S, Sen HN, Colyer M, Zapor M, K Wroblewski. Update on ocular tuberculosis Curr Opin Ophthalmol. 2101; 23: 551-556.
8. D.V. Vasconcelos-Santos, M. Zierhut, N.A. Rao. Strengths and weaknesses of diagnostic tools for tuberculous uveitis. Ocul Immunol Inflamm, 2009 ; 17: 351-355
9. Rao NA, Saraswathy S, Smith RE. Tuberculous uveitis: distribution of Mycobacterium tuberculosis in the retinal pigment epithelium. Arch Ophthalmol. 2006;124:1777–1779
10. Sharma P, Bansal R, Gupta V, Gupta A. J Ophthalmic Inflamm Infect. 2010; 11:1(1): 23-7.
11. M. Ang, H.M. Htoon, S.P. Chee. Diagnosis of tuberculous uveitis: clinical application of an interferon-gamma release assay Ophthalmology 2009; 116 :1391-1396
12. Wroblewski K. J, Hidayat AA, Neafie RC, Rao NA, Zapor M. Ocular tuberculosis: a clinicopathologic and molecular study. Ophthalmology. 2011; 118: 772-777.