Review Article

A review on Ocular Tuberculosis: Epidemiology, Clinical features and Treatment

~~**ABSTRACT :**~~**ABSTRACT:**

Background: The globalisation and migration movements are intimately linked to the expansion of tuberculosis. Tuberculosis has also been the major cause of death in patients with HIV infection, as well as the leading cause of death related to antibiotic resistance. Tuberculosis may affect any part of the uveal tract. T cell activity is of significance in Tuberculous infection. The phagocytosis of bazillion by macrophage is a major factor in limiting the spread of infection. However in patients who have had a previous tuberculous infection, the cell mediated response is also associated with tissue damage due to direct effect of sensitized T lymphocytes on cell containing the ingested bacilli. Ocular tuberculosis is a type of extrapulmonary tuberculosis with a wide range of symptoms. Tuberculosis is considered to infect the lungs of the patients in 80% of cases, and the 20% of cases affecting other organs like the eye. Ocular tuberculosis is an infectious disease with bacterial aetiology that has a chronic case with a poor prognosis. Even the most effective treatment can cause a loss of vision, and clinical recovery is not always permanent. Ocular tuberculosis frequently results in permanent impairment, lowering patients' quality of life.

~~**Objective :**~~**Objective:** This article reports the various known presentations of ocular TB and reviews important elements of ~~epidemiology ,~~epidemiology, diagnosis and treatment.

~~**Methodology :**~~~~The~~**Methodology: The** present study is a systematic review of literature searched from electronic databases and highly reputed websites like PubMed~~, researchgate~~, researchgate, elsevier ~~etc~~etc ~~.~~., Medical Subject Headings (MeSH) and the trial registry in English language.

Conclusion: Ocular tuberculosis (OTB) diagnosis and treatment are difficult to come by. The disease's current state of uncertainty is due to mixed ocular tissue involvement, a lack of consensus on best ~~practise~~ practice diagnostic tests, and global variations in medical management. The present evaluation intends to provide an update on OTB's recent progress.

~~**Keywords :**~~**Keywords:** tuberculosis, ocular tuberculosis, orbital tuberculosis, eye infections and visual acuity.

Introduction:

Around 1.7 billion people are diagnosed with ~~tuberculosis.Tuberculosis~~tuberculosis. Tuberculosis is a severe social health problem that affects people all around the world. According to the World Health Organization (WHO), tuberculosis is the most common cause of death worldwide, with tuberculosis being the sole infectious agent to ~~blame.This~~blame. This organism is an obligate ~~aerobes,slow~~aerobes, slow growing, non-spore ~~forming,non~~forming, on-mobile bacterium.

In many developing countries, TB is the most frequent opportunistic infection among HIV-positive individuals, owing to poor sanitation, hygiene, treatment resistance, and poverty. Tuberculosis was identified in 24% patients out of 450 HIV infected adults who were examined in a recent research done in Cambodia from January 2004 to February ~~2005 .~~2005. Around

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15% of newly diagnosed patients with tuberculosis will also have HIV-positive testing, according to a Chicago ~~study ,~~study, implying a relationship between TB and HIV. WHO recommends treating HIV infection with tuberculosis as "two diseases - one patient" and providing full treatment.[1]

Multiple organs in the body can be affected by tuberculosis. Rare variant of extrapulmonary tuberculosis is ocular tuberculosis that should not be overlooked due to the possibility for loss of vision in patients. Due to its diverse clinical signs, such as mixed ocular tissue involvement, lack of gold standard testing, diagnostic criteria, and lack of agreement on therapy strategy, OTB remains a major diagnostic and therapeutic challenge.[3]

OTB can develop as a primary infection (with the eye as the entrance point) or as a result of hematogenous dissemination.[4]

The most prevalent ocular symptom of the disease is occlusive retinal vasculitis, multifocal serpiginous choroiditis and granulomas are the most common Ocular Tuberculosis lesion. [4]

Etiology:

Ocular tuberculosis caused by any of the following ways:-

1. Direct infection due to an exogenous source although uncommon, primary exogenous eye Infection can arise in the lids or conjunctiva. Cornea, Sclera, and lacrimal sac are other exterior tissues that are less usually affected.
2. Hematogenous spread because of its high vascular load, the uveal tract which is the most commonly implicated eye's coat.
3. Hypersensitivity reaction in structure of the eye due to some other forms of ocular tuberculosis like phylectenular disease and Eale's disease.

Alan Woods was the first to apply Rich's law to ocular TB and classify it into four separate groups (22). The following is a summary of Woods' four categories.

A reaction that is similar to that of a foreign body[2].

1. Sclerokeratitis or Eales' disease are examples of acute restricted inflammation that can reoccur if the patient's diminishes resistance.

2. Repeated recurrences of chronic inflammation.

3. Acute, quickly spreading inflammation characterised by necrosis, caseation, and, on rare occasions, tuberculous panophthalmitis.

The most prevalent kind of ocular involvement is hematogenous spread. Seeding can happen as a result of a primary infection or a dormant lesion reactivating.[5]

Aerosolized droplets are used to spread *M. tuberculosis*. Inhaled microorganisms engage alveolar macrophages in the respiratory alveoli. It is primarily an air borne disease and spreads from one person to another person by coughing and sneezing. Approximately 1 to 5 micron droplets suspended in air for several hours. Usually 5 to 200 inhaled bacteria is sufficient to cause infection. About 90% of infected people are asymptomatic or latent TB. About 5% of the remaining 10% will get sick during the first several years of exposure. As host immunity deteriorates, the remaining 5% may show symptoms years later.

M. tuberculosis avoids eradication by preventing phagolysosome fusion, despite the fact that bacteria are phagocytosed by alveolar macrophages and emit some cytokines to draw circulating monocytes to the infection site.This allows the bacteria to multiply in macrophages that aren't fully activated or partially active. Through erosions in the alveolar epithelium, bacteria-laden macrophages eventually disperse to the lymphatic and venous circulation and travel to the oxygen-rich areas of the body~~.~~, example: apex of lungs, various organs, and the eye.[5]

Epidemiology:

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An incidence is reported of ocular involvement varies, depending on the criteria used for diagnosis and the sampled population.[2]
On the basis of epidemiology, ocular morphologies, and positive supporting tests like Purified Protein Derivative PPD or Interferon Gamma Release Assay IGRA, the major population are diagnosed with presumptive ocular TB.[3]
According to the Centers for Disease Control and Prevention (CDC), *Mycobacterium tuberculosis* infects one-third of the world's population, or nearly two billion people, and 10% of those infected will get ill at some point in their lives. Extrapulmonary signs include 16–27% of patients, including those with orbital and external eye ~~illness.India~~illness. India, China, Japan, Thailand, Philippines are the most densely populated Asian Pacific Countries with prevalence of Ocular TB as 0.4-9.8% , 4%, 7%, 2.2% and 6.8% respectively.[6]
Ocular TB is not common in the general population, but it is treated in referral centres on a regular basis.
Donahue reviewed the ophthalmic records of over 10,000 with primary pulmonary~~ TB~~ TB who were inspected in the eye clinic of the Mattapan ~~Sanatorium ,~~Sanatorium, in Boston, Massachusetts,~~ USA~~ USA. He analysed 154 (1.4%) patients with ocular TB.[7]
Bouza and his colleagues discovered that eye tuberculosis was more common in Spain; 100 patients were randomly selected and observed in a emergency clinic; 18 had eye injuries, which includes choroiditis,retinitis, and scleritis.[1]
Rosen et al described 12 individuals with intraocular tuberculosis~~, 9~~, 9 of which had retinal vasculitis, 2 had choroidal ~~tubercle ,~~tubercle, and 1 had chronic anterior uveitis~~, in~~, in a more recent series published in 1990.

Pathophysiology:
Attempts to understand the pathophysiology of OTB have proven to be substantially more difficult than clinical discoveries. Even though the mechanism of *Mycobacterium tuberculosis* dissemination has been difficult to ~~prove,it~~prove, it is widely thought that hematogenous M.tb dissemination to the eye causes intraocular inflammation but the molecular evidence of M.tb is very rare to be found in the given sample of ocular fluid.
In diverse kinds of granulomatous uveitis,the diagnostic effectiveness of traditional polymerase chain reaction (PCR) for M.tb is as low as 37.7%. Despite significant advancements in molecular diagnostic techniques over the year,the routine Mtb Polymerase chain reaction utilization has still modest.[8]
Humans are the only natural host. End organs with high oxygen tension i.e lungs apices,kidney,bone,meninges,eye are typically infected. In the eye ciliary body and choroid are mainly affected.
Causes of mycobacterium tuberculosis on the eye is determined by mechanism of infection. Extraocular involvement indicates that the patient has a primary ocular infection caused by direct contact with the eye.
The iris and anterior part (ciliary body) as well as the choroid make up the uveal tract (posteriorly), is most usually affected by TB dissemination from pulmonary or extrapulmonary locations (posteriorly).When M. tuberculosis-infected macrophages enter the eye, they deposit in the first available capillary beds, causing posterior uveitis, which is commonly occurring ocular TB symptom. Bacilli grow and cause local inflammation, resulting in the formation of a choroidal tubercle.
Pathogenesis of ocular tuberculosis are classified in 5 stages which are as follows:
In stage 1, Alveolar macrophages phagocytosis bacteria which can either lead to its growth or it may get destroyed. If bacteria grows it will destroy the macrophages and form initial nidus of developing tubercle.

In stage 2, circulating monocytes are deposited at nidus where they are phagocytosed but not destroyed.
In stage 3, bacteria-laden macrophages are destroyed due to delayed type of hypersensitivity and it will lead to tissue damage causing caseous necrosis.
In stage 4, if the response of delayed type of hypersensitivity is poor it may break open into lymphatic and blood vessels.
In stage 5, liquefaction of caseous necrosis and erosion of bronchial wall occurs.

Clinical features:
History
In recent ~~years ,~~years, immunocompromised persons have been found to be at the highest risk of getting ocular tuberculosis with more than half of the total individuals with AIDS and tuberculosis having the extrapulmonary involvement.
Therefore whenever we are suspecting ocular ~~TB ,~~TB, it is critical to obtain a detailed prior medical and social history, as well as to question about the patient's HIV status.[10]

Presenting signs and symptoms :
Extra ocular ~~involvement :~~involvement:
This type of infection is acquired either through direct inoculations followed by haematogenous dispersion or through a hypersensitive reaction. On the outside of the eye the extra -ocular sign of tuberculosis can be seen as persistent blepharitis, lid abscess or atypical chalazion.[11]

Orbit
Based on its performance ocular tuberculosis can be classified into 5 groups:
Orbital periostitis which causes erythema and Ed's a of conjunctiva and lid as well as involvement of the vascular structure of the orbit.[12]
~~1)In~~1) In long-term situations, it can also appear as cortical abnormalities that progress to thickening and sclerosis of the orbital bones.[13]
2) Tuberculosis of soft tissue of the Orbit without bone degeneration
3) Orbital tuberculosis with bone involvement in which it can present as as proptosis secondary to the mass effect
4) Paranasal sinus is responsible for orbital spread.
5) Inflammation of the lacrimal gland[12].

Skin of the eyelids and peri orbital area:
In children involvement of the eyelids is most commonly seen. The TB on the eyelid might manifest as lid abscess, persistent blepharitis or atypical chalazion(nodules resembling chalazion) on the outside of the eye .When pressure is applied to the skin of the eyelids, it resembles lupus vulgaris, with red-brown nodules that blanch to a "apple jelly" hue. The clinical form is thought to be an add-on of the tuberculosis affecting the skin which include subepithelial protuberance,plaque and ulcers as symptoms.[11]

Conjunctiva:
Inflammation of the thin membrane covering the eyeball and lining the eyelid,subconjunctival nodules, polyps, tuberculomas, and ulcers are all symptoms of conjunctival tuberculoma. While conjunctivitis has become more widely popular w.r.t the context of systemic disease, the atypical conjunctivitis with no systemic signs has been documented.Phlyctenulosis can also be caused by an exaggerated hypersensitive response which isn't always linked to infection.[13]Reddening of eyes, distress, suppuration of mucus and ~~pus ,~~pus, and swelling of the eyelids, are the widely prevalent clinical presentations.[11]

Sclera:
Tuberculosis is responsible for around 10.6% of cases of Infectious Scleritis.[11] Ocular symptoms of tuberculosis include scleritis and scleral nodules. Episcleral nodules may occur as a result of the reaction with mycobacterial proteins. Scleritis comes in two forms:nodular and diffuse, with nodular scleritis being the most prevalent. The sclera can weaken or possibly perforate as a result of the lesion's necrosis.[12]

Cornea:
Involved corneal patients may experience photalgia, and their exams may reveal profound stromal keratitis and corneal ~~erosions.Patients~~erosions. Patients may develop mycobacterial infections as a result of the body's immunological reaction to the bacteria which can further lead to interstitial keratitis, disciform keratitis, and phlyctenular keratoconjunctivitis. [13]

Investigation:
There are various Investigation which are as follows:
1) Histopathological evidence:
Acid fast bacilli on direct smear or culture of mycobacterium T.B from the given sample. This is the gold standard and conclusive method but also has limited sensitivity, delayed diagnosis due to bacteria's slow growth.
2) Tuberculin skin ~~test(~~test (TST)~~:This~~; This method is used for determining whether M T.B Infection is latent or active based on immunological evidence. It is low cost and easy to access.
3) Interferon-Gamma Release assay:
Is the test that is used to measure the amount of Interferon Gamma released into the body. It is more specific, resistant to atypical mycobacteria and unaffected by prior BCG immunization. But there are some drawbacks also which include low sensitivity, very expensive, and quite burdensome. It also cannot differentiate between latent and active forms of the disease.
~~4)PCR~~4) ~~:~~PCR: It is a method which is used to detect the genome of Mycobacterium even from a tiny sample of ocular fluid. It provides fast detection and quantification of pathogen burden in samples with minimum danger of carryover and cross contamination. It can also be used to detect drug resistant mycobacterium strain.
~~5)Chest~~5) Chest X-ray: When lungs are the dominant location of tuberculosis infection, this method is used to examine patients with suspected tuberculosis intraocularly.
~~6)Fluorescein~~6) Fluorescein ~~angiography:It~~angiography: It is mainly used to determine retinal vascular leakage and active choroidal lesion.[14]

Treatment:

Generally, the treatment for ocular tuberculosis is comparable to the active pulmonary and extrapulmonary tuberculosis in which there are four drugs regimen which include Rifampicin, Isoniazid, Pyrazinamide and Ethambutol which are provided for two months on a daily basis and then continued for a period of four months.[5]
Patients with pulmonary tuberculosis who shows sign of medication resistance are moved to a different regimen based on culture ~~results,the~~results, the same can be done if drug resistant is detected in patients with increasing ocular infection.[14]
Oral steroids are definitely a complicating issue mainly in patients with suspected tuberculous uveitis. The inflammation worsened or recurred in patients who were only given systemic corticosteroids.[5]
Reassessment of patients every two to three months should be done for the following:-[15-22]
~~1. Control~~1 Control and reduction of inflammation

~~2 Reducing~~2 Reducing the use of corticosteroids
~~3 Reduction~~3 Reduction in the outburst of illness and rate of recurrence or decreasing the severity and prolonging the illness free period.
Central Fibres of optic nerves are usually affected, resulting in impaired or loss of vision, reduced visual acuity and patients are unable to identify red and green color.
Ethambutol is a common antibacterial agent ~~against actively~~against actively growing T.B bacilli. It acts by preventing cell walls from forming.
Optic neuropathy is the most well known Ethambutol toxicity, which is widely thought to be rare and reversible in medical literature.[16] Ethambutol is contraindicated in optic neuritis because renal illnesses is a risk factor for optic neuropathy since Ethambutol is excreted through kidney.[17]

Conclusion:
Due to tuberculosis~~, ophthalmologist~~, ophthalmologist can expect cases of disease if population sample is very large. Assessing the degree of dissemination of the disease is also a very important role which is done by an ophthalmologist. Eye T.B is not a contagious disease. Scleritis and other ocular Inflammatory symptoms may be caused by tuberculosis particularly latent type. Delayed diagnosis can result in eye sight loss and infection related systemic problem.

References:

1. Abdisamadov A, Tursunov O. Ocular tuberculosis epidemiology, clinic features and diagnosis: A brief review. Tuberculosis (Edinb). 2020 Sep;124:101963. doi: 10.1016/j.tube.2020.101963. Epub 2020 Jul 21. PMID: 32745954.
2. Albert DM, Raven ML. Ocular Tuberculosis. Microbiol Spectr. 2016 Nov;4(6):10.1128/microbiolspec.TNMI7-0001-2016. doi: 10.1128/microbiolspec.TNMI7-0001-2016. PMID: 27837746; PMCID: PMC5180603
3. Testi I, Agrawal R, Mehta S, Basu S, Nguyen Q, Pavesio C, Gupta V. Ocular tuberculosis: Where are we today? Indian J Ophthalmol. 2020 Sep;68(9):1808-1817. doi: 10.4103/ijo.IJO_1451_20. PMID: 32823397; PMCID: PMC7690544.
4. Teixeira-Lopes F, Alfarroba S, Dinis A, Gomes MC, Tavares A. Ocular tuberculosis - A closer look to an increasing reality. Pulmonology. 2018;24(5):289-293. doi:10.1016/j.pulmoe.2018.02.006
5. https://www.ncbi.nlm.nih.gov/books/NBK559303/#_NBK559303_pubdet_
6. Win MZA, Chee SP. Epidemiological Aspect of Ocular Tuberculosis. In: Kumar A, Chawla R, Sharma N, editors. Ocular Tuberculosis, Essentials in Ophthalmology. Cham: Springer; 2017, pp.1-6.
7. Alvarez GG, Roth VR, Hodge W. Ocular tuberculosis: diagnostic and treatment challenges. Int J Infect Dis. 2009 Jul;13(4):432-5. doi: 10.1016/j.ijid.2008.09.018. Epub 2009 Apr 22.
8. Basu S, Elkington P, Rao NA. Pathogenesis of ocular tuberculosis: New observations and future directions. Tuberculosis. 2020 Jul 24:101961.
9. Neuhouser AJ, Sallam A. Ocular Tuberculosis. [Updated 2021 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559303/
10. Khadka P, Kharel R (2019) Ocular tuberculosis: Clinicopathologic assortment and diagnostic challenges. J Clin Res Ophthalmol 6(1): 011-020. DOI: 10.17352/2455-1414.000057

11. Yan WJ, Zhou HY, Yan H. Characterization of and advanced diagnostic methods for ocular tuberculosis and tuberculosis. *Int J Ophthalmol*. 2020;13(11):1820-1826. Published 2020 Nov 18. doi:10.18240/ijo.2020.11.21
12. Dalvin LA, Smith WM. Orbital and external ocular manifestations of Mycobacterium tuberculosis: a review of the literature. Journal of clinical tuberculosis and other mycobacterial diseases. 2016 Aug 1;4:50-7.
13. https://www.aao.org/topic-detail/ocular-tuberculosis-tb--asia-pacific-2
14. Figueira L, Fonseca S, Ladeira I, Duarte R. Ocular tuberculosis: position paper on diagnosis and treatment management. Revista Portuguesa de Pneumologia (English Edition). 2017 Jan 1;23(1):31-8.
15. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. InMayo Clinic Proceedings 2003 Nov 1 (Vol. 78, No. 11, pp. 1409-1411). Elsevier.
16. https://eyewiki.aao.org/Ethambutol_Optic_Neuropathy
17. Abbafati, Cristiana, Kaja M. Abbas, Mohammad Abbasi, Mitra Abbasifard, Mohsen Abbasi-Kangevari, Hedayat Abbastabar, Foad Abd-Allah, et al. "Five Insights from the Global Burden of Disease Study 2019." LANCET 396, no. 10258 (October 17, 2020): 1135–59.
18. Abbafati, Cristiana, Kaja M. Abbas, Mohammad Abbasi, Mitra Abbasifard, Mohsen Abbasi-Kangevari, Hedayat Abbastabar, Foad Abd-Allah, et al. "Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019." LANCET 396, no. 10258 (October 17, 2020): 1204–22.
19. Franklin, Richard Charles, Amy E. Peden, Erin B. Hamilton, Catherine Bisignano, Chris D. Castle, Zachary Dingels V, Simon Hay I, et al. "The Burden of Unintentional Drowning: Global, Regional and National Estimates of Mortality from the Global Burden of Disease 2017 Study." INJURY PREVENTION 26, no. SUPP_1, 1 (October 2020): 83–95. https://doi.org/10.1136/injuryprev-2019-043484.
20. James, Spencer L., Chris D. Castle, Zachary Dingels V, Jack T. Fox, Erin B. Hamilton, Zichen Liu, Nicholas L. S. Roberts, et al. "Estimating Global Injuries Morbidity and Mortality: Methods and Data Used in the Global Burden of Disease 2017 Study." INJURY PREVENTION 26, no. SUPP_1, 1 (October 2020): 125–53. https://doi.org/10.1136/injuryprev-2019-043531.
21. James, Spencer L., Chris D. Castle, Zachary Dingels V, Jack T. Fox, Erin B. Hamilton, Zichen Liu, Nicholas L. S. Roberts, et al. "Global Injury Morbidity and Mortality from 1990 to 2017: Results from the Global Burden of Disease Study 2017." INJURY PREVENTION 26, no. SUPP_1, 1 (October 2020): 96–114. https://doi.org/10.1136/injuryprev-2019-043494.
22. Lozano, Rafael, Nancy Fullman, John Everett Mumford, Megan Knight, Celine M. Barthelemy, Cristiana Abbafati, Hedayat Abbastabar, et al. "Measuring Universal Health Coverage Based on an Index of Effective Coverage of Health Services in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019." LANCET 396, no. 10258 (October 17, 2020): 1250–84. https://doi.org/10.1016/S0140-6736(20)30750-9.