

Ocular Manifestations among Systemic Tuberculosis Cases: A Hospital Based Study from Nepal

Subash Bhatta^{1*}, Ajit Thakur², Dev Narayan Shah³, Meenu Choudhary³, Nayana Pant³

¹Geta Eye Hospital, Kailali, Nepal

²Drishti Eye Hospital, Jhapa, Nepal

³Institute of Medicine, Kathmandu, Nepal

Email: *subashbhatta@gmail.com

How to cite this paper: Bhatta, S., Thakur, A., Shah, D.N., Choudhary, M. and Pant, N. (2019) Ocular Manifestations among Systemic Tuberculosis Cases: A Hospital Based Study from Nepal. *Journal of Tuberculosis Research*, 7, 202-211.

<https://doi.org/10.4236/jtr.2019.74019>

Received: August 23, 2019

Accepted: October 26, 2019

Published: October 29, 2019

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Abstract

Aim: To study the frequency of various ocular manifestations in diagnosed cases of active pulmonary and extra pulmonary tuberculosis in two different major hospitals in Nepal. **Method:** A hospital based, cross sectional descriptive study was conducted in the National Tuberculosis Centre, Bhaktapur and BP Koirala Lions Center for Ophthalmic Studies (BPKLCOS), Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal during a period of 18 months from February 2010 to August 2011. Diagnosed cases of systemic tuberculosis were evaluated by ophthalmologists for any ophthalmic manifestations. **Results:** There were 585 cases in the study. 399 (68%) were cases of pulmonary tuberculosis and 186 (32%) were that of extra pulmonary tuberculosis. Ocular manifestations were seen in 2.6% (15 patients) of the study population; 1.25% (6 patients) in cases of pulmonary tuberculosis and 5.37% (9 patients) in extra pulmonary tuberculosis cases. Uveitis (40%) followed by papilloedema (33%) were the two most common ocular manifestations. Of the 25 affected eyes of 15 patients, 2 eyes of patients with choroiditis involving the macular area were legally blind. Majority of the affected cases (67%) had bilateral involvement. **Conclusion:** Ocular manifestations in tuberculosis vary greatly ranging from mild episcleritis to potentially blinding posterior uveitis, clinical acumen being of great importance in timely diagnosis and treatment so that vision threatening complications can be prevented. Ocular manifestations are more common in extra pulmonary tuberculosis cases.

Keywords

Tuberculosis, Ocular Tuberculosis, Uveitis, Choroiditis, Papilledema

1. Introduction

Tuberculosis is an infectious disease of chronic pathology caused by one of the members of the *Mycobacterium tuberculosis* complex that includes *M. tuberculosis*, *M. bovis*, and *M. africanum* (most commonly by *M. tuberculosis*). This disease is characterized by formation of granulomas. *M. tuberculosis* is an obligate aerobic slow growing, non-spore forming, and non-motile bacterium. The disease is spread through airborne aerosol gaining access in the lung, resulting in a latent or dormant infection in susceptible hosts. Globally, there is an estimated 9.6 million new cases and 1.5 million deaths are attributed to TB. About 58% of cases are in the South-East Asia and Western Pacific regions. In Nepal alone there are 44,000 new cases and 60,000 people living with TB, with 4900 death a year [1].

Ocular tuberculosis encompasses any infection by *Mycobacterium tuberculosis* complex involving the eye. Terms as “primary” and “secondary” ocular tuberculosis are often used in literatures. There is difference in opinion regarding definition of primary ocular tuberculosis (TB). Some literatures use it to describe isolated ocular disease without systemic involvement, while others use the term when eye is the initial port of entry of the bacilli. The term, secondary ocular tuberculosis is reserved for those cases where there is ocular involvement from seeding by hematogenous spread from primary sites as lungs and lymph nodes. There can also be direct invasion from surrounding areas like paranasal sinus or cranial cavity. Difficulty in obtaining ocular tissue for biopsy often makes it difficult to establish a conclusive diagnosis by demonstrating tuberculosis bacteria in tissue and hence the diagnosis is frequently presumptive [2] [3]. Delayed hypersensitivity reaction to tuberculosis bacteria without the presence of any infectious agent can lead to ocular disease. This makes the evaluation of ocular fluid sample less sensitive to any laboratory examinations. There is also lack of uniform diagnostic criteria in addition to the difficulties in confirming the diagnosis with traditional laboratory methods [3]. Hence epidemiological data on the true prevalence of ocular TB is scanty and varied in different parts of the world [4] [5] [6].

Consequences of tuberculosis in eye can lead to permanent blindness in patients. It's therefore necessary to identify the ocular manifestations of early stages of the disease. In spite of vast developments in diagnostic tools, evidence of systemic tuberculosis disease along with suggestive clinical ocular findings is still considered the major diagnostic criteria for ocular tuberculosis, more so over in a developing country like Nepal where such modern diagnostic facilities are often limited. Thus the knowledge about frequency and clinical features of ocular tuberculosis in Nepalese population can be of huge benefit in diagnosing such cases early and providing the patient with proper treatment. As to our knowledge, no study has yet been reported from Nepal evaluating the ocular manifestations in tuberculosis patients. Hence this study was done to evaluate ocular findings in diagnosed cases of pulmonary and extra pulmonary tuberculosis so as to find out the frequency and types of ocular manifestations seen in tubercu-

losis.

2. Subjects and Methods

A hospital based, cross sectional descriptive study was conducted in National tuberculosis Centre, Bhaktapur, Nepal (center for tuberculosis control in South East Asia region) and BP Koirala Lions Center for Ophthalmic Studies (BPKLCOS), Tribhuvan University Teaching Hospital (TUTH), Kathmandu Nepal during a period of 18 months from February, 2010 to August 2011 after approval from institutional review board of Institute of Medicine.

The study was explained to all eligible people in their own language, and consent was obtained. Patients with history suggestive of tuberculosis were first examined by general physicians. Clinical examination was done, followed by relevant investigations. Three morning samples of sputum for AFB staining were taken along with a chest X-ray postero-anterior view. Diagnosis of pulmonary TB was made on the basis of at least 2 sputum samples staining positive for AFB or one sample positive with suggestive X-ray findings. Smear negative pulmonary tuberculosis was diagnosed on the basis of relevant history, suggestive X-ray findings and positive Mantoux test with no improvement after a week of appropriate antibiotic therapy. Extra pulmonary tuberculosis was diagnosed by direct tissue cytology in most cases. In those cases where tissue wasn't accessible for cytology evaluation, findings suggestive of tuberculosis on relevant imaging studies and positive supporting evidences as Mantoux test, IgM Quantiferon Gold and serum immunoglobulin IgG and IgM assay were taken into consideration in making a diagnosis.

Detail ocular evaluation of the cases was then conducted by an ophthalmologist. Visual acuity was assessed by Snellen Vision Chart with multiple optotypes. Any evidence of ocular misalignment and abnormality of extra ocular movement was evaluated with extra ocular motility and cover tests. Periorbital area and anterior segment was first examined with diffuse torchlight. Haag Streit 900 slit lamp was used in appropriate magnification and illumination for further evaluation of anterior and posterior segment. Posterior vitreous and fundus were evaluated under dilatation using 90 diopters and 20 diopters Volk aspheric lenses. Gonioscopy was done as required. Fundus fluorescein angiography and optical coherence tomography were done in cases with choroidal manifestations. Uveitis cases were evaluated for signs of granulomatous or non-granulomatous inflammation with recording of type and distribution of keratic precipitates, anterior chamber reaction, posterior synechiae and iris nodules. Vitreous was examined for cells and exudates. Snow balls, snow banking and peripheral sheathing were also looked for. Any evidence of posterior uveitis like choroidal tubercles, tuberculoma, subretinal abscess, serpiginous-like choroiditis or endophthalmitis was noted. Any signs of retinal vasculitis and optic nerve abnormalities like papilloedema or optic neuropathy were also evaluated. Cases of uveitis were further evaluated by a uveitis specialist. Data was analysed using SPSS 14 software. The frequencies of ocular manifestations were evaluated with chi square test sta-

tistical for significance level.

3. Results

The mean age of presentation was 35.76 years with the range of 3 - 78 years. There were total of 585 cases enrolled in the study. 60% (349) of the cases were males and 40% (236) were females. 68% (399) of enrolled patients were cases of pulmonary tuberculosis and 32% (186) were extra pulmonary cases. Lymph node TB (26%) was the most common presentation among extra pulmonary cases followed by pleural effusion (21%) and TB meningitis (17%).

Cases with Ocular Manifestations: Among 585 cases of tuberculosis, 2.56% (n = 15) were found to have some form of ocular manifestations.

Table 1 shows the age and gender distribution of tuberculosis cases with ocular manifestation. 87% (n = 13) of the involved cases were younger than 30 years of age with 40% (n = 6) of patients in the age group of 11 - 20 years. Ocular manifestations were more common in younger patients with tuberculosis. (p = 0.05, chi square test). Although females constituted only 40% of the total cases, 47% (n = 7) of the cases with ocular manifestations were females. 53% of the ocular manifestations were seen in males (p = 0.053, z = 1.93)

Table 2 shows the ocular manifestation according to site of tuberculosis. Despite the majority (68%) of cases in our study being those of pulmonary tuberculosis, only 5 (1.25%) of them had ocular manifestations. 10 cases (5.37%) of extra pulmonary tuberculosis had ocular manifestations (p < 0.0001, z = 40.20). Among those with ocular manifestations, 47% percent of manifestations were observed in cases with tubercular meningitis.

Table 3 shows the visual acuity of affected eye in snellen acuity. 67% (n = 10) of the affected cases had bilateral involvement. Of the 25 affected eyes of 15 patients, 84% (n = 21) had best corrected visual acuity (BCVA) between 6/6-6/18. 12% (n = 3) of affected eyes had BCVA less than 6/60. BCVA was less than 3/60 in 2 eyes with posterior uveitis involving the macular area.

Table 4 describes the Types of Ocular Manifestations in affected case. Of the 15 cases having ocular manifestations; the most common ocular manifestation was uveitis, observed in 40% (n = 6) of the involved cases. All forms of uveitis were observed. Posterior uveitis was the most common form of uveitis comprising 50% of uveitis cases.

Table 1. Age and sex distribution of cases with ocular manifestations.

	Age group	0 - 10	11 - 20	21 - 30	31 - 40	41 - 50	>50	Total
Pulmonary	M	0	2		1	0	0	3
	F	0	0	2	0	0	0	2
Extra Pulmonary	M	1	2	2	0	0	0	5
	F	1	2	1		1	0	5
Total		2	6	5	1	1	0	15

Table 2. Distribution of affected cases according to types of Tuberculosis.

Type of tuberculosis	Number	Percentage (%)
TB meningitis	7	47
Pulmonary TB	5	33
Gland TB	2	13
Brain TB	1	7

Table 3. Visual status of the affected eyes of cases with ocular involvement.

Visual acuity	VA in affected eye (n)
6/6-6/18	21
<6/18-6/60	1
<6/60-3/60	1
<3/60	2

Table 4. Ocular manifestations in cases of TB.

Manifestations	No. of cases	Percentage (%)
Anterior	1	
Anterior + Intermediate	1	
Uveitis	6	40
Posterior	3	
Panuveitis	1	
Papilloedema	5	33
LR paresis	2	13
Recurrent nodular scleritis	1	7
Recurrent nodular episcleritis	1	7
TOTAL	15	100

Papilloedema was the second most common ocular manifestation seen in 33% of cases. All of those cases were of tubercular meningitis. Two cases of LR paresis (1 case of unilateral and 1 case of bilateral LR paresis) with associated raised intracranial pressure were also seen. There was a case each of recurrent nodular scleritis and episcleritis. The distribution of patients with type of ocular manifestation is given in **Figure 1**.

4. Discussion

Tuberculosis is one of the major causes of morbidity and mortality in Nepal. This disease has serious public health implications. Survey suggests that a significant number of people in productive age group suffer from Tuberculosis in Nepal [7]. In this study of 585 cases of tuberculosis, majority (68%) of cases were of pulmonary tuberculosis; however the number is lower than that of national statistics [1]. The higher number of extra pulmonary cases in the study compared

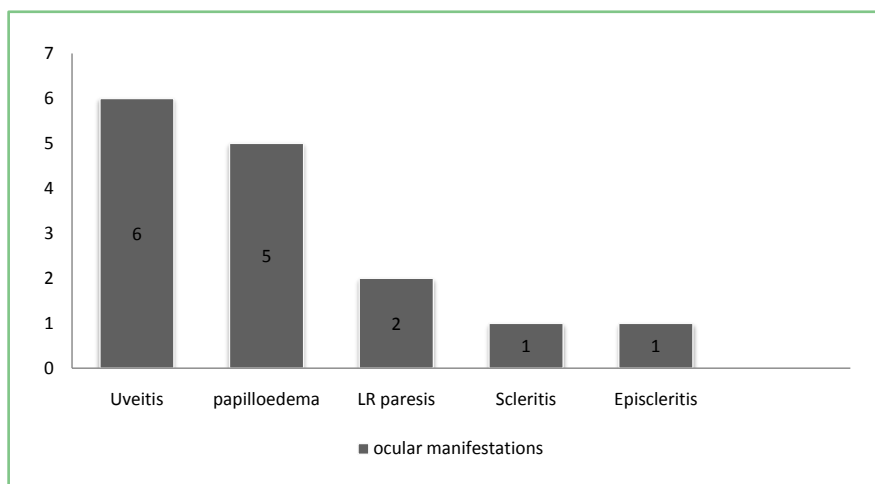


Figure 1. Profile of TB cases with ocular manifestation.

to the national statistics may be due to the fact that all our cases were seen in tertiary level referral centers where extra pulmonary cases like tubercular meningitis and others which need more advanced facilities for diagnosis and management are encountered more frequently.

The literatures from different countries have varying reports on prevalence of ocular manifestations in tuberculosis [4] [5] [6]. The prevalence seen in our study (2.56%) is higher than that reported by a study (1.39%) conducted in a neighboring country where ocular morbidity pattern in 2010 eyes of 1005 patients with active pulmonary and extra pulmonary tuberculosis were studied prospectively [4]. This may be attributed to greater percentage of complicated tubercular meningitis cases seen in our study. We found greater percentage of ocular manifestations in such cases.

Cases with ocular involvement showed no significant sex preponderance. Sahu *et al.* reported similar finding with 56.36% of the cases with ocular involvement to be females and the most common involved age group in their study was between 15 - 30 years [8]. Our study also showed younger population to be frequently involved. The common age group with ocular manifestations in our study was 11 - 20 years (6 cases, 40%) followed by 21 - 30 years (5 cases, 33%), with the mean age of presentation being 20.4 years. This is in accordance with general disease pattern of systemic tuberculosis which mainly affects younger age group of population [1].

Though pulmonary tuberculosis is more common than extra-pulmonary tuberculosis, ocular manifestations were commonly seen in cases of extra pulmonary tuberculosis (67%). Literatures have suggested that majority of patients with extrapulmonary TB do not have any evidence of pulmonary TB [9] [10].

Uveitis (40%) followed by papilledema (33%) was the most common ocular manifestation in our study. Tuberculosis was observed to be the second most common identifiable cause of uveitis in a large review looking at reports from several countries [11]. Uveitis is the most common ocular manifestation in tu-

berculosis as uvea receives the most share of blood supply in eye [12]. In a case series from Srilanka, eighteen out of twenty-three patients with symptomatic ocular TB had tuberculous uveitis [13]. In a study by Biswas *et al.*; the most common ocular finding was bilateral healed focal choroiditis (50%) [4]. In another study from India where 55 cases of ocular tuberculosis were evaluated, the most common ocular finding was acute anterior uveitis (21.8%) [8]. Tubercular uveitis can result from direct infection or immune-mediated hypersensitivity response to mycobacterial antigen. It can present as granulomatous or non-granulomatous anterior uveitis, intermediate uveitis, vitritis, retinal vasculitis, neuroretinitis, solitary or multiple choroidal tubercles, multifocal choroiditis, choroidal granulomas, subretinal abscess, endophthalmitis, and panophthalmitis and hence can mimic multiple uveitis etiologies [2] [3]. Of the 158 patients with presumed diagnosis of intraocular tuberculosis in India (1994 to 2004), 66 (42%) cases had posterior uveitis, 57 (36%) cases were having anterior uveitis, 18 (11%) cases had panuveitis, and the remaining 17 (11%) were categorized as having intermediate uveitis [2]. In our study we observed one case of non granulomatous anterior uveitis, one case having both anterior and intermediate uveitis with features of granulomatous inflammation, three cases of posterior uveitis and one case of panuveitis. Posterior uveitis was found to be the most common finding among cases of tuberculosis uveitis in various other studies [14] [15]. However TB uveitis can present in any anatomical part of eye with varying manifestations from non-granulomatous anterior uveitis to occlusive retinal vasculitis [16].

All cases had bilateral presentations except for two cases of posterior uveitis having unilateral presentation. Bilateral nongranulomatous anterior uveitis was seen in a case of pulmonary tuberculosis. There was a case of anterior and intermediate uveitis in a patient with pulmonary tuberculosis presenting with bilateral mutton fat keratic precipitates and Koeppe's nodules on iris. Snow banking was seen with peripheral venous sheathings. Another case of pulmonary TB presented as panuveitis with non-granulomatous inflammation. Of three cases with posterior uveitis, two cases had choroiditis involving the macular area. One was a case of pulmonary tuberculosis and the vision in affected eye was 2/60. Another case had tubercular cervical lymphadenitis. Vision was 1/60 in the involved eye. A case presented with multiple tubercles in both eyes, sparing the macular region. Lesions were yellowish, noncontiguous; about the size of one fourth of the disc diameter with indistinct margins. These lesions were not associated with vitritis. She was a known case of multiple brain tuberculomas.

Choroidal tubercles are clinically white, gray, or yellow lesions. Borders are generally indistinct with surrounding edema. Size can vary from about one third disc diameter to two disc diameters. They can be single or multiple. Sahu *et al.* reported choroiditis in 6 (10.90%) cases and anterior uveitis in 12 (21.81%) cases [8]. In Malawi, Africa, 2.8% incidence of choroidal granuloma was reported among 109 patients with fever and tuberculosis [17].

Choroidal tubercles are common findings among tuberculosis manifestations

in eye.

Of five patients with papilloedema in our study, all were below 20 years of age, the youngest being three years of age. The findings of papilloedema as second common ocular manifestation in tuberculosis in our study can be explained on the basis of relatively large number of complicated tubercular meningitis cases especially children, referred to us from different centers. In a study from Malawi; out of 109 patients with TB, two patients had papilloedema, one with pulmonary tuberculosis and one with TB meningitis [17]. Tuberculosis is one of the common etiologies of meningitis in Nepal, more so in children. In persons who develop tubercular meningitis, there is hematogenous seeding of bacilli to the meninges or brain parenchyma. This results in formation of subpial or subependymal foci of metastatic caseous lesions which have propensity to enlarge and rupture into the subarachnoid spaces, leading to meningitis. Basal meningitis can lead to obstructive hydrocephalus from obstruction of basilar cisterns leading to papilloedema. In children, primary optic atrophy and blindness can result from direct involvement of the optic nerves and chiasma by basal exudates (*i.e.*, opticochiasmatic arachnoiditis). In adults, long standing papilledema will commonly lead to secondary optic atrophy. Papilloedema is considered to be poor prognostic factor for tuberculous meningitis [18].

Basal meningitis leads to cranial nerve pathologies resulting in paresis or palsy. Sahu *et al.* described 1 (1.81%) case of cranial nerve palsy out of 55 cases of ocular tuberculosis [8]. In our study, out of 31 cases of tubercular meningitis, we had two cases of cranial nerve paresis (14% of all cases with ocular involvement), both with involvement of VI nerve, one of them having bilateral lateral rectus paresis. Sharma *et al.* also reported CN VI to be most commonly affected cranial nerve in tubercular meningitis [19].

Anterior non necrotizing nodular scleritis was observed in a case of lymph node tuberculosis in our study. There was nodular episcleritis in a patient with pulmonary tuberculosis with history of multiple recurrences even after treatment with topical steroids. Sahu *et al.* reported scleritis and episcleritis to be common occurrences among cases of ocular tuberculosis with 12 cases (21%) of scleritis and 2 cases (4%) of recurrent episcleritis among 55 cases of ocular tuberculosis [8]. A case series of ocular Tuberculosis from Srilanka also reported a case of episcleritis and inflammatory scleral nodule [13]. Tuberculous scleritis may lead to scleromalacia [20]

Tuberculosis is one of the existing pandemic diseases in the world that can affect almost every organ of the body. Despite the low percentage of ocular manifestation in TB, ocular morbidity due to tuberculosis is still in significant numbers because of high prevalence of tuberculosis among people in developing countries. Newer diagnostic tools as PCR showing mycobacterial load in intra-ocular fluids in combination with ophthalmic features of tuberculosis help in diagnosis of ocular tuberculosis [21]. As sophisticated diagnostic tools are still not available in most of the developing countries and they too cannot alone make a definitive diagnosis; clinical features are still the most important criteria

for making a diagnosis of ocular tuberculosis. This study helps in outlining some of the common manifestations that patients with ocular tuberculosis can present with. It is very important for clinicians to be well aware of these different manifestations of tuberculosis in eye so as to make an early diagnosis and start the correct treatment before the patient suffers from irreversible loss of vision. As tuberculosis is mainly a disease of young people, proper ophthalmic examination of tuberculosis patients is recommended for early diagnosis and treatment; preventing significant years of productivity that can be lost due to visual disability having a tremendous impact on wellbeing of a society.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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