



ORIGINAL RESEARCH PAPER

Pulmonary Medicine

PROFILE OF EXTRA PULMONARY TUBERCULOSIS- A FIVE YEAR RETROSPECTIVE STUDY IN A TERTIARY CARE HOSPITAL.

KEY WORDS: Eptb, Rntcp, Vitamin D Deficiency

C.Mohan Rao	Asst. Professor, Dept. of Respiratory Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar.
Saswat Subhankar*	Senior Resident, Dept. of Respiratory Medicine, Kalinga Institute of Medical Sciences, , Bhubaneswar *Correspondent Author
A.K. Mohapatra	Asst. Professor, Dept. of Respiratory Medicine, Kalinga Institute of Medical Sciences, Bhubaneswar.
Debee Prasad Dash	Professor and HOD, Dept. of Respiratory Medicine, Kalinga Institute of Medical Sciences, ,Bhubaneswar.

ABSTRACT

BACKGROUND Extra-pulmonary TB (EPTB) is a significant health problem . We wanted to evaluate the spectrum of the site of extra-pulmonary involvement in a tertiary health care centre inhabited by tribals and slum dwellers around its vicinity. We also wanted to evaluate the status of blood Vitamin D levels in selected patients.
METHOD 470 EPTB cases diagnosed between 2013 and 2017 from 840 TB treatment records maintained in RNTCP centre.
RESULTS AND CONCLUSION Among the 470 EPTB cases (55.9%), lymph node followed by pleura and abdomen were the organs having maximum involvement. There was male preponderance . Blood Vitamin D level was lower in lymph node (mean = 11.77ng/ml; SD= 4.5753) than pleura(mean = 14.52ng/ml; SD= 12.1903). Patients with a low BMI had lower levels of vitamin D (mean= 10.57ng/ml; SD = 4.1881). Adults had lower vitamin D levels than pediatric population (mean= 10.8ng/ml; SD 5.07). Timely treatment can prevent morbidity among EPTB victims.

INTRODUCTION

Tuberculosis is common among the low socioeconomic strata of the population and under-privileged social groups in the country .They have high level of under nutrition . Poverty,migration for education, job are the factors that compel them to migrate to cities,metropolitan areas.They settle in slums in overcrowded dwellings, these factors influence the spread of communicable disease including tuberculosis.(1). The challenge of inaccessibility to health services and their health care seeking behaviour seem to dominate their health. The impact of Tb is higher involvement involving extra pulmonary sites and the vulnerable patients are infants and children.They also suffer from diseases due to malnutrition. (2,3).

As per Global report by WHO in 2016 around 10.4 million people contracted tuberculosis (4).In India about 2.2 million people contract TB each year and approximately 220,000die from the disease(5).Incidence rate of TB is 167(156-179)/1 lakh/year,prevalence 195(131-271)/1 lakh (6), prevalence in tribal population (2011 unpublished) 80/1 lakh.

As per programme performance in 2014, number of new bacteriologically confirmed pulmonary TB cases was 7,54,202, number of clinically diagnosed new PTB cases 3,43,032, number of bacteriological confirmed relapse cases 1,24,670, number of clinically relapse cases 1,12,066 and number of extra pulmonary new TB cases 2,75,502. The numbers are a cause of concern for India(7).

Tuberculosis of any part of the body other than lung is defined as extra-pulmonary tuberculosis; this entity is a common opportunistic infection with people living with HIV and AIDS. However it is also witnessed in other immune-compromised states such as Diabetes Mellitus and malnutrition. The burden of EPTB has increased from 17% to 21% over a period of 10 years . Better diagnostic availability has lead to increased reporting. Prevalence of EPTB is also higher in pediatric age group(8). There is also significant regional variation across the country. In Delhi, 32% of all cases of TB in 2011 were reported to be EPTB cases and the same increased to 35.4% in 2013(9,10). This assumes significance in the context of drug resistant TB.

Micro-nutrients as potential adjunctive immuno-protective therapy has been attracting medical attention because of

evidence of anti-mycobacterial activity of vitamin D3. The biologically active form of vitamin D has been shown to affect innate immunity by modulating macrophage function; this may enhance protection against tuberculosis infection.Vitamin D also upregulates antimicrobial peptide cathelicidin and enhances killing of intracellular M. tuberculosis Economically weaker sections who may be suffering from malnutrition including possible deficiency of micro-nutrients may also have concomitant Vitamin D deficiency due to additional poor exposure to sunlight in slums. In order to have some assessment of status of Vitamin D deficiency(VDD). Some EPTB cases who had volunteered underwent serum Vitamin D estimation.

Kalinga Institute of Medical Sciences(KIMS) ,a tertiary health care centre and a medical college, is also a designated microscopy centre under R..N.T.C.P, caters to the health management of local population residing in its adjacent locality slums among whom tribals and economically weaker section constitute majority. The area in its vicinity is an educational and commercial hub.

It is important to revisit the burden and distribution of extra pulmonary TB in these vulnerable communities, that to our knowledge has not been carried out in recent times.Failure in early diagnosis and treatment may result in serious socioeconomic problems through significant ill health and lasting disability.

AIM OF THE STUDY

Primary Objective:

To study the pattern of extra-pulmonary TB diagnosed in the clinical suspects who attended our institute, for evaluation.

Secondary Objective

To evaluate the outcome following supervised anti tubercular chemotherapy given in full duration after diagnosis.

MATERIALS AND METHODS

Extra pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis involving organs other than the lungs e.g.pleura, lymphnode, abdomen, genito-urinary tract, skin, joint and bones, meninges etc.

Study Period: EPTB cases diagnosed during 2013-2017 .

Study type: Retrospective study from the medical records of diagnosed cases in our institute during above mentioned period.

Sample size: Considering the incidence rate of TB in India 167(156-179) per one lakh population per year with proportion of EPTB TB cases around 15%-20%, the sample size would be around 175 cases over 5 year period. However initial scrutiny of records during 2013-2017 reveal around 470 EPTB cases were diagnosed and registered for treatment.

Inclusion Criteria: RNTCP registered eligible EPTB cases residing around the vicinity of KIMS (Designated Microscopic Centre)

Exclusion Criteria: 1. Cases with pulmonary involvement.
2. Cases with HIV co-infection.

Method: The cases satisfying the inclusion criteria only were considered in the study. These cases were mainly diagnosed by imaging techniques such as chest x-ray, ultrasound, CT and MRI scans, FNAC and smear for AFB and histo-pathological study of biopsy material from the involved organs.

All the cases were diagnosed by concerned consultants as per the investigations mentioned above, and referred to D.O.T.S center for registration. All the cohorts were followed for full completion of the chemotherapy under supervision and the outcome recorded.

The five year data of the cases were collected from inpatient and outpatient department record and DOTS centre at KIMS including demographics, clinical presentation, and treatment outcome. The vitamin D levels were obtained from some of these records, in patients who had voluntarily agreed to undergo the evaluation. Reference range of vitamin D level was 20-60 ng/ml.

Statistical analysis: Summary statistics for all the categorical clinical parameters were presented as frequency and percentage. As the subgroup sample size is very small, categorical characteristics were compared between the two groups using Fischer's exact test. A p-value of <0.05 was considered as statistically significant. All the analysis was carried out using standard statistical significant STATA 15.1.

RESULTS

Out of the registered 840 TB cases, 470 (55.9%) involved extra-pulmonary sites. The major site of predilection of the involvement in extra-pulmonary organs were lymph node (n=249; 52.9%) followed by pleura (n=122; 24.9%), abdomen (n=40; 8.5%) spine (n=24; 5.2%), bone (n=18; 3.9%), eye (n=9; 1.9%), disseminated (n=5; 1%) and CNS (n=3; 0.7%).

Table 1: Site Of Involvement Of Extrapulmonary Tb (2013-2017)

SITE	FREQUENCY	PERCENTAGE (%)
LYMPH NODE	249	52.9
PLEURA	122	25.9
SPINE	24	5.2
BONE	18	3.9
ABDOMEN	40	8.5
DISSEMINATED	5	1
EYE	9	1.9
CNS	3	0.7

Males constituted majority of the EPTB cases (55.3%). In the age group of 4-14 yrs there were 65 males and 49 females where as in the age range of more than 15 yrs group there were 195 males and 164 females.

Out of total 249 cases of lymph node tuberculosis 134 were male and 115 were female. In 122 pleural tuberculosis cases, there were 66 males and 56 females respectively. Children in the age range of 4-14 yrs were victims of lymph node and pleural tuberculosis in about 50% cases.

Tuberculosis of spine, bone, abdomen were encountered more commonly in ≥ 15 yrs age group (21, 13, 25 cases respectively) than 4-14 yrs age group (3, 5, 15 cases respectively). Disseminated TB was seen in 3 cases in 4-14 yr age group compared to 2 cases in ≥ 15 yrs age range. Tuberculosis of eye was more witnessed in age range of more than 15 yrs (6 cases) than 4-14 yrs age (3 cases).

Vitamin D levels was performed in 30 cases out of which 6 were males and 24 females (M:F= 1:5). Most of the patients were more than 15 yrs. of age. The mean vitamin D level was less in patients ≥ 15 yrs. (10.8 ng/ml; SD 5.07) (p= 0.1359).

Table 2: Site Predilection In Relation To Age And Gender (n=470)

PATTERN		LN	PLEURA	SPINE	BONE	ABDOMEN	DISSEMINATED	EYE	CNS	TOTAL
4-14yrs	TOTAL	42	42	3	5	15	3	3	1	114
	MALE	24 (36.9%)	22 (33.8%)	2 (3.1%)	3 (4.6%)	9 (13.8%)	2 (3.1%)	2 (3.1%)	1 (1.54%)	65
	FEMALE	18 (36.7%)	20 (40.8%)	1 (2.0%)	2 (4.1%)	6 (12.2%)	1 (2.0%)	1 (2.0%)	0 (0.0%)	49
	p-value	0.984	0.445	1.00	1.00	0.802	1.00	1.00	1.00	
≥15yrs	total	207	80	21	13	25	2	6	2	356
	MALE	110 (56.4%)	44 (22.6%)	12 (6.1%)	11 (5.6%)	13 (6.7%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	195
	FEMALE	97 (60.2%)	36 (22.4%)	9 (5.6%)	2 (1.2%)	12 (7.4%)	1 (0.6%)	3 (1.9%)	1 (0.6%)	161
	p-value	0.465	0.963	0.822	0.043	0.772	1.00	1.00	1.00	
GRAND TOTAL		249	122	24	18	40	5	9	3	470

* p<0.05 is significant

Table 3: Comparison Of Vitamin D Level And Sex Between Different Age Group (n=30).

CHARACTERISTICS	AGE GROUP		P value
	4-14yrs (N=13)	≥15yrs (N=17)	
SEX; N (%)			
MALE	3 (50.0%)	3 (50.0%)	1.00
FEMALE	10 (41.7%)	14 (58.3%)	
VITAMIN D LEVEL (NG/ML); (MEAN ± SD)	15.14±10.17	10.8±5.04	0.136

* p<0.05 is significant

Of the 30 cases, 20 (66.67%) had tubercular lymphadenopathy

while 10 (33.3%) had pleural involvement. Vitamin D levels were observed to be less in patients who had tubercular lymphadenopathy (mean = 11.77 ng/ml; SD = 4.5753) (p = 0.3749).

Table 4: Vitamin D Level And Pattern Of Disease (n=30)

TYPE OF DISEASE	Frequency (%)	Vitamin D Level (ng/ml); (Mean ± SD)	P value
LYMPHADENOPATHY	20 (66.67%)	11.77 ± 4.57	0.375
PLEURAL EFFUSION	10 (33.3%)	14.52 ± 12.19	

Most of the patients had a normal BMI (53.3%). However, patients with a low BMI had lower levels of vitamin D (mean = 10.57 ng/ml; SD = 4.1881) (p = 0.17).

Table 5: Correlation Of Vitamin D Level And Bmi (n= 30)

BMI (kg/m ²)	Frequency (%)	Vitamin D Level (ng/ml); (Mean ± SD)	P value
<18.5	14 (46.67%)	10.57 ± 4.19	0.172
18.5-24.9	16 (53.3%)	14.53 ± 9.80	

* p<0.05 is significant

All 470 cases registered for D.O.T.S ,CAT I regimen was advised for 422 cases while CAT II regimen was prescribed for 48 cases respectively.Among the CAT I regimen prescribed for 422 cases,415 (98.3%) were declared treatment completed while 7 (1.7%) defaulted. In case of CATII regimen prescribed for 48 cases, 37(77%) were declared treatment completed, 8(16.7%) defaulted while 3(6.3%) died.

Table 6: Treatment Outcome 2013-2017 (N= 470 Cases)

	Total	Completed treatment	Relapse	Failure	Default	Death
CAT I	422	415			7	
CAT II	48	37			8	3

DISCUSSION

In our series, 55.9% cases were diagnosed as EPTB which was much higher than the RNTCP National Data of 15 -20 percent. Similar observations were reported by Gonzalez et al who reported 538 EPTB cases out of total 1878 tuberculosis cases(11),Aysel Sunnetcioglu where there were 203(49.4%) EPTB cases out of 411 cases(12) and Tahir et al 48% who reported 722 EPTB cases out of 1490 TB cases (13). This is due to improved awareness among the clinicians and availability of new diagnostics in the extra- pulmonary presentations and awareness to register in RNTCP services for availing the services. The role model played by medical colleges cannot be overemphasized as they are pioneer in RNTCP framework Similar observations were reported from study by H C Maltezou in their assesment of 102 children with Extrapulmonary tuberculosis where they found not only 50% increase of admission for EPTB cases over past decade but also majority had superficial lymphadenitis (n-48), pleural effusion (n-27)(14).

EPTB was witnessed more commonly among males (54.6%) than female (45.4%). Similar observations were made in the study by Ramaprakash and colleagues who documented 51.52%(15) and Mavila R et al who reported 112(59.9%) males as sufferers of extra-pulmonary TB out of 187 cases diagnosed in their study period (16).This could be due to alcohol abuse,outdoor exposure in daily life, occupation etc. The lower notification rate in females might be due to under-diagnosis,or under reporting of tuberculosis as a result of various social stigma and impaired access to health care(17).Biological factors can also influence opportunities for exposure to M.tuberculosis (18).

In our series lymphnode involvement was the most common site(52.9 %) followed by pleura(25.9%). Similar results were reported by Ilgazli et al who witnessed 56.3% lymphnode involvement followed by 31.1% pleural involvement outof 636 cases with EPTB (19). This raises the possibility that higher transmission of infection during early years of life compounded with malnutrition and over crowding that have been held responsible for these outcomes.

Lower blood level of Vitamin D was observed in our population, mostly in adults (≥ 15yrs.), lymph node TB and then pleural involvement and in patients with a low BMI but did not reach statistical significance . Undernourished tribals and slum-dwellers who remain in overcrowded dwellings are more prone to lack of exposure to sun and deficient in nutrition which may include Vitamin D. This may probably make them susceptible to tuberculosis. This is reflected in low serum level of vitamin D in our series along with low body mass index among the tuberculosis cases.

Vitamin D upregulates antimicrobial peptide cathelicidin and enhances killing of intracellular M.tuberculosis. In the absence of

adequate vitamin D level,triggering toll-like receptors of macrophage by M.tuberculosis antigen results in impaired production of cathelicidin (20,21,22,23,24). Shan Ju Huang et al in their meta analysis found Vit D deficiency was significantly associated with increased risk of tuberculosis(OR= 2.57;95% CI={1.34,3.80};p<0.00001),subgroup analysis in Asian population revealed similar results(OR =2.62; 95%CI= {1.63,4.23}; p< 0.0001).As sunlight and diet are two major sources of vitamin D for humans. Adequate exposure to sunlight and/or diet supplementation will maintain adequate vitamin D level in the body(25).

The 98.3%success rate in out come of chemotherapy in CAT I and 77% in CAT II cases needs further strengthening of supervisory services under RNTCP.

CONCLUSION

EPTB accounted for a major proportion of tuberculosis cases in the current study.It is a significant health problem in tribals and other economically deprived population. Common site of predilection were lymphnode and pleura . Male preponderance amongst the EPTB cases was notable. Lymph node TB cases had lower vitamin D level than pleural TB . Low BMI patients had witnessed more vitamin D deficiency than normal BMI patients in this extra-pulmonary group.

LIMITATIONS

1. Clinical profile of the EPTB cases not studied.
2. Blood vitamin D level not studied in all subjects. As observed sample size is small, further a larger study may be more clinically relevant to validate the study.

Funding:Nil

Conflict of Interest: Nil

Permission from Institutional Ethics committee: Yes

Acknowledgements: We are thankful to Dr. Bhaskar Thakur, Asst. Professor (Statistics), Dept. Of Community Medicine and RNTCP Staff, KIMS, Bhubaneswar for their support.

References

1. Olson NA,Davidow AL,WinstonCA.etal, A national study of socioeconomic status and tuberculosis rates by country of birth,United States,1996-2005.BMC Public Health.2012;18:12-65.
2. Government of India.The National Tribal Policy(Draft):A Policy for the Scheduled Tribes of India2006.Available from http://www.legalpundits.com?content folder/tribalpolicy.pdf.
3. Basu,SK.A health profile of tribal India,Health Millions.1994;2:12-4(Pubmed)
4. .WHO global tuberculosis report.2016.Available at:http:// www.who .int/tb/ publications/global_report/en/.
5. TB India 2016 revised national TB control programme annual status report, New Delhi 2016(Cited Sept 2016) Available at:www.tbindia.nic.in
6. TB India 2017.RNTCP status Report.Central TB division,Directorate General of Health Services,Ministry Of Health and Family Welfare,Nirman Bawan,New Delhi,2017
7. WHO.Tuberculosis Control In South East Asia Region,Regional Report,2016
8. Arora VK,Gupta R. Directly observed treatment for tuberculosis.Indian J paedtr 2003;70:885-889.
9. TB India 2012.RNTCP Status Report,Nirman Bhavan,New Delhi 11011,Central TB division ,Directorate General Of Health Services,Ministry of Health and Family Welfare;2012:116-117.TB India2014,pp.67-8
10. TB India 2014. RNTCP Status Report,Nirman Bhavan,New Delhi 11011,Central TB division ,Directorate General Of Health Services,Ministry of Health and Family Welfare;2014:67-68
11. Gonzalez OY, Adams G, Teeter LD,Bui TT,Musser JM,Gravis EA. Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis.Int J Tuberc Lung Dis. 2003;7:1178-85.
12. Aysel Sunnetcioglu,Mahmut Sunnetcioglu, irfan binici, Ali irfan baran et al, comparative analysis of pulmonary and extra pulmonary tuberculosis of 411 cases, annals of clinical microbiology and antimicrobials 2015;14:34 (published online 2015 jun 24.
13. Tahir M, Sharma SK, Rohrberg D, Gupta D, Singh UB, Sinha K, DOTS at a tertiary care centre in northern india : success , challenges and the next steps in TB control. Indian J Med Res 2006;123:702-6
14. H C Maltezou, P Spyridis, D A Kafetzis. Extrapulmonary tuberculosis in children. Arch Dis Child 2000;83:342-346.
15. Rama Prakasha S,Suresh G, Ganesh Kumar S. Mapping the pattern and trends of Extrapulmonary Tuberculosis.J Glob Infect Dis.2013;5(2):54-9.
16. Rajani Mavila, Manoj Kottarath, Smitha Nair, Milan malik Thaha. Int J Res Med Sci.2015 Nov;3(11):3386-3390.
17. Yang Z,Kong Y,Wilson F,Foxman B,Fowler AH,Marrs CF, et.al. Identification of risk factors for extra pulmonary tuberculosis, Clin Infect Dis.2004;38:199-205.
18. Martinez AN,Rhee JT,Small PM,Behr MA.Sex differences in the epidemiology of tuberculosis in San Francisc,Int J Tuberc Lung Dis,2000,vol.4(pp26-31).
19. Ilgazli A,Boyaci H,Basyigit I,Yildiz F. Extrapulmonary tuberculosis :Clinical and epidemiologic spectrum of 636 cases. Arch Med Res. 2004;35:435-41.
20. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: Vitamin D-mediated human

- antimicrobial activity against *Mycobacterium tuberculosis* dependent on the induction of cathelicidin. *J Immunol.* 2007;179:2060–3. [PubMed]
21. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol.* 2010;10:482–96. [PubMed]
 22. Najeeha Talat, Sharon Perry, Julie Parsonnet, Ghaffar Dawood, and Rabia Hussain. Vitamin D Deficiency and Tuberculosis Progression. *Emerging Infectious Diseases.* www.cdc.gov/eid Vol. 16, No. 5, May 2010.
 23. Selvaraj P. Vitamin D, vitamin D receptor, and cathelicidin in the treatment of tuberculosis. *Vitam Horm.* 2011;86:307–25. [PubMed].
 24. PK Sasidharan, E Rajeev, Perintalmanna, V Vijayakumari. Tuberculosis and Vitamin D deficiency in Kerala, India. *Medicine Update* 2012; 331-35.
 25. Shao- Jun Huang, Xian-Hua wang, Zhi –Dong Liu, Wen-Li Cao, Yi Han, Ai –Guo, Ma and Shao-Fa xu. Vit D deficiency and the risk of tuberculosis : a meta analysis. *Drug Des Devel Ther.* 2017;11:91-102,, published on line 2016 Dec 28.