International Journal of Research in Medical Sciences
Rao CM et al. Int J Res Med Sci. 2018 Oct;6(10):3375-3380
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20184049

Original Research Article

Pattern of extra pulmonary tuberculosis among urban population with special reference to CBNAAT as a diagnostic tool: a retrospective study at a tertiary care hospital of Odisha, India

C. Mohan Rao[1]*, Bhaskar Thakur[2], Saswat Subhankar[1], D. P. Dash[1]

[1]Department of Respiratory Medicine, [2]Department of Community Medicine, Kalinga Institute of Medical Sciences, KIIT Deemed to be University, Bhubaneswar, Odisha, India

Received: 31 July 2018
Accepted: 29 August 2018

***Correspondence:**
Dr. C. Mohan Rao,
E-mail: dr.cmrao55@gmail.com

ABSTRACT

Background: Diagnosis of Extra-pulmonary TB (EPTB) is a challenge. Authors wanted to assess the sites of extra-pulmonary involvement during 2013-2017 in a tertiary care hospital cum medical college. Authors also wanted to evaluate the role of Cartridge Based Nucleic Acid Amplification Test (CBNAAT) in diagnosis of EPTB and compare its efficacy with AFB Culture.
Methods: Total 470 EPTB cases diagnosed between 2013 and 2017 from 840 TB treatment records maintained in designated microscopy centre. Specific samples from appropriate sites were taken up for smear for AFB, CBNAAT and AFB culture.
Results: There was incremental detection and registration in both TB and EPTB cases from 96 and 50 cases in 2013 to 246 and 150 cases in 2017 respectively. Among the total 470 EPTB cases in 2013-2017 (55.9%), lymph node followed by pleura and abdomen were the organs having maximum involvement. Bone involvement was more witnessed in adult male than children ($p < 0.05$). There was male preponderance. CBNAAT results were 100 % sensitive and 87.5% specific. Lymph node samples and pus elsewhere in the body had much better diagnostic yield than serous effusions.
Conclusions: Awareness and availability of diagnostic services in tertiary care institutions has lead to increased reporting of EPTB under RNTCP services. CBNAAT can be also be utilized as a point of care testing for lymph node aspirate and pus specimen.

Keywords: CBNAAT, EPTB, RNTCP

INTRODUCTION

Extra pulmonary Tuberculosis is a protean disease affecting virtually all the organs. It is common in the low socioeconomic section of the population.[1] The impact of TB is higher with greater involvement of extra pulmonary organs in this vulnerable population.[2,3]

Globally around 10.4 million people contract tuberculosis.[4] Of these in India there were an estimated 2.8 million new cases and 0.48 million deaths due to TB in 2015.[5] Incidence rate of TB is 167(156-179)/1 lakh/year. In 2014-number of clinical diagnoses of new PTB and EPTB were 3,43,032 and 1,12,066, respectively. It is a cause for concern in India.[6]

Extra-pulmonary tuberculosis is a milder form of disease in terms of infectivity as compared to pulmonary tuberculosis. It is common in people living with HIV and AIDS, and also witnessed in malnutrition victims.

Prevalence is also higher in paediatric age group.[7] Better diagnostic availability has led to increased reporting of the disease. Following haematogenous spread of bacilli during primary pulmonary infection, EPTB may develop later in any anatomic location.[8] Once the diagnosis has been considered, confirmation can be difficult, with sample collection from deep-seated tissues being challenging and the disease typically being pauci-bacillary.

In April 2017, Indian EPTB guidelines have been developed as evidence-based practice for suspecting, diagnosing and managing EPTB in medical care services. CBNAAT (Xpert MTB/RIF) is a commercially available test for M. tuberculosis complex (MTB) which uses polymerase chain reaction (PCR) to test specimen for genetic material specific to MTB and simultaneously detects a gene (rpoB) which confers resistance to rifampicin.[9,10]

This diagnostic facility is available at the Regional Medical Research Centre (ICMR), Bhubaneswar. Both respiratory and non-respiratory specimens are accepted for CBNAAT study. Kalinga Institute of Medical Sciences (KIMS), a tertiary care centre caters to the health needs of local population residing in its vicinity. It has a designated microscopy centre.

Authors, in this study, wanted to evaluate the site predilection, demographics of EPTB involvement. The diagnostic utility of CBNAAT in extra-pulmonary specimens was also evaluated, which is first of its kind in Odisha after its clinical utility in TB Control Programme in 2017.

Primary objective

To study the pattern of extra pulmonary TB diagnosed in the clinical suspects who attended KIMS, Bhubaneswar for evaluation.

Secondary objective

To evaluate the diagnostic utility of CBNAAT in extra-pulmonary specimens in selected cases in 2017.

METHODS

Extra pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis involving organs other than the lungs e.g. pleura, lymph node, abdomen, genito-urinary tract, skin, joint and bones, meninges etc. Study period was EPTB cases diagnosed during 2013-2017. Retrospective study from the medical records of diagnosed cases in our institute during above mentioned period. 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 years 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

- Cases with pulmonary involvement
- Cases with HIV co-infection.

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 DOTS center for registration. All the cohorts had been followed for full completion of the chemotherapy under supervision and the outcome recorded.

The five years 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 cases for which CBNAAT was performed for diagnosis were considered as a subgroup in the study.

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 Fisher's exact test. Sensitivity and specificity of CB NAAT was also computed. A p value of <0.05 was considered as statistically significant. All the analysis was carried out using standard statistically significant STATA 15.1.

RESULTS

The number of cases of tuberculosis and EPTB cases registered in 2013 were 96 and 50 respectively, that has increased to 246 and 150 in the year 2017 (Table 1).

Among 840 cases registered for treatment 470 (55.90%) had EPTB. Among the EPTB cases male constituted 54.6% (257 cases) compared to 45.6% females (213 cases) (Table 3). The major site predilection was in the following sequence: lymph node (249, 52.9%) followed by pleura (122, 24.9%), abdomen (40, 8.5%), spine (24, 5.2%), bone (18, 3.9%), eye (9, 1.9%), disseminated (5, 1%) and CNS (3, 0.7%) (Table 2).

Lymph node and pleura were the most commonly affected extra-pulmonary organs in both the age groups. Tuberculosis of spine, bone, abdomen was more commonly encountered in more than 15 yrs age group (21,13 and 25 cases respectively) than 4-14 yrs age group. Tuberculosis of Eye was more witnessed in age range of more than 15 yrs (6 cases) than 4-14 yrs age (3 cases) (Table 4).

Table 1: Year wise distribution of cases in percentage of involvement of extra pulmonary sites.

Year	No. of TB cases registered	No. of EPTB cases registered	%	LN %	Pleura %	Spine %	Bone and joint %	Abdomen%	Disseminated %	Eye %	CNS %
2013	96	50	52	42	32	4	2	6	4	8	2
2014	109	76	69	60	21	0	1.3	13	1.3	-	2.6
2015	176	80	46	80	10	-	1	3.7	2.4	-	-
2016	213	114	53	39	30	8.7	4.3	14	-	2.6	-
2017	246	150	60	48	30	8	6.6	5	2	-	-

Table 2: Site of involvement of extra-pulmonary TB (2013-2017).

Site	No. of ex-pulmonary TB case registered	Frequency	Percentage (%)
Lymphnode	470	249	52.9
Pleura	470	122	25.9
Spine	470	24	5.2
Bone	470	18	3.9
Abdomen	470	40	8.5
Disseminated	470	5	1
Eye	470	9	1.9
CNS	470	3	0.7

Pleural fluid was the most common sample for which CBNAAT was performed (38.1%) followed by lymph node aspirate (23.8%).

Table 3: Site of involvement in EPTB sites in relation to gender (2013-2017).

Site	Male	Female	Total
Lymphnode	134 (53.8%)	115 (46.2%)	249
Pleura	66 (54%)	56 (46%)	122
Spine	14 (58.3%)	10 (41.7%)	24
Bone	11 (61%)	7 (39%)	18
Abdomen	22 (55%)	18 (45%)	40
Disseminated	3 (60%)	2 (40%)	5
Eye	5 (55.5%)	4 (44.5%)	9
CNS	2 (66.6%)	1 (33.4%)	3

Lymph node aspirate and pus provided the highest CBNAAT positive cases (Table 5). All the samples were put for mycobacterial culture. The sensitivity and specificity of CBNAAT against culture were detected to be 100% and 87.5% respectively (Table 6).

Table 4: 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

Of 470 cases registered for DOTS, 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 7).

Table 5: CBNAAT results from extra-pulmonary samples.

Site		Smear for AFB		CB NAAT		AFB culture	
	Total	POS	NEG	POS	NEG	POS	NEG
Lymph node aspirate	15	8	7	7	8	4	11
lymph node pus	8	2	6	3	5	1	7
Tissue from lymph node	3	0	3	1	2	0	3
Tissue from skin	3	0	3	1	2	0	3
Pus from bone	3	1	2	2	1	2	1
Pus from breast	1	0	1	0	1	0	1
Pleural fluid	24	0	24	0	24	0	24
CSF	5	0	5	0	5	0	5
Peritoneal fluid	1	0	1	0	1	0	1
Total	63	11	52	14	49	7	56

Table 6: Diagnostic indices of CB NAAT compared with the AFB culture.

	AFB culture (positive)	AFB culture (negative)	Total	
CB NAAT Positive	7	7	14	Sensitivity=100%
CB NAAT Negative	0	49	49	Specificity= 87.5%
Total	7	56	63	

Table 7: Treatment outcome 2013-2017.

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

DISCUSSION

The study was done to evaluate the pattern of extra-pulmonary TB over a 5 years period. The number of patients diagnosed from 2013 reveal steady increase in numbers till 2017; this is due to improved awareness among the clinicians and availability of new diagnostic modalities in the extra pulmonary presentations and awareness to register in RNTCP services for availing the services. Similar results were reported by Pandit S et al.[11] The role model played by medical colleges cannot be over-emphasized as they are pioneer in RNTCP framework. Involvement of extra-pulmonary site as a percentage of total TB cases registered was much higher than the RNTCP National data of 15-20 percent. Similar observations were reported by Gonzalez et al, (538 EPTB cases out of total 1878 tuberculosis cases), Aysel Sunnectcioglu et al, (49.4% EPTB cases), Tahir et al, (722 EPTB cases out of 1490 TB cases).[12-14]

Among the total EPTB cases lymph node involvement was highest of about 52.9% followed by pleura (25.9%); this raises the possibility that higher transmission of infection during early years of life compounded with malnutrition and overcrowding had been responsible for these outcomes. Similar observations were reported from study by Maltezou HC et al, in their assesment of 102 children with extra-pulmonary tuberculosis where they found not only 50% increase of admission for EPTB cases over past decade but also that majority had superficial lymphadenitis (n=48) and pleural effusion (n=27).[15]

EPTB was more witnessed in male (54.6%) than female (45.4%). Similar observations were made in the study by Ramaprakash et al, who documented 51.52% males and Mavila R et al, who reported 112 (59.9%) male as sufferers of extra-pulmonary TB.[16,17]

In present series, lymph node 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% lymph node involvement followed by 31.1% pleural involvement out of 636 cases with EPTB.[18]

CBNAAT results of EPTB specimen revealed higher diagnostic yield from lymph node aspirate and pus compared to no detection from pleural fluid, CSF and peritoneal fluids. This could be explained by the hypersensitivity phenomenon; because few organisms are present in the pleural space, this is a Cell Mediated Immunity phenomenon. In such cases pleural fluid culture results are positive in 20-40% of patients with

proven tubercular pleuritis.[19,20] However, in our series the overall CBNAAT sensitivity was 100% and specificity was 87.5%.

Denkinger et al, in a meta-analysis identified 18 studies involving 4461 samples, where they found Xpert sensitivity differed substantially between sample types. In lymph node tissues or aspirates Xpert pooled sensitivity was 83.1% (95% CI 71.4-90.7%) versus culture and 81.2% (95%CI 72.4-87.7%) versus composite reference standards (CRS). In pleural fluid sensitivity was 46.4% (95% CI, 26.3-67.8%) against culture and 21.4% (95% CI 8.8-33.9%) against CRS. CSF sensitivity was 80.5% (95% CI 59.0-92.2%) against culture and 62.8% (95% CI 47.7-75.8%) against CRS. Xpert pooled sensitivity was consistently 98.7% against CRS across different sample types.[21]

Similarly, a study by Lawn SD et al, revealed sensitivity of CBNAAT exceeded 75% for tissue biopsies and fine needle aspirate (88.3%; 95% CI: 82-95) gastric aspirate (78.7%; 95% CI: 68-89), pus samples (87.3%; 95% CI: 67-100), CSF (85.7% ;95% CI: 67-100) and urine (87.5% ;95% CI :71-100). Lowest sensitivity was observed in pleural fluid samples (44.4%; 95% CI: 21-67), and other body fluids including pericardial, peritoneal and synovial fluids (50%; 95% CI: 19-81).[22]

Limitation of the study was a greater number of cases to undergo CBNAAT test for better diagnostic predictability.

CONCLUSION

EPTB needs a high index of suspicion and judicious invasive diagnostic tests. There was a high detection rate of EPTB cases over a five-year period. Lymph node followed by pleura, abdomen and bone were the most common sites of involvement. Male preponderance was noticed. CBNAAT had a high diagnostic yield in cases of lymph node aspirates and pus. Thus, CBNAAT can be utilized as a point of care testing in these samples.

ACKNOWLEDGEMENTS

Authors would like to thank staff of KIMS DMC, Dr. Dasarathi Das, Scientist-E, Regional Medical Research Center (ICMR), Bhubaneswar, Odisha.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Olson NA, Davidow AL, Winston CA, Chen MP, Gazmararian JA, Katz DJ. A national study of socioeconomic status and tuberculosis rates by country of birth, United States, 1996-2005. BMC Public Health. 2012 Dec;12(1):365.
2. Government of India. The National Tribal Policy (Draft). A Policy for the Scheduled Tribes of India; 2006. Available at: http://www.legalpundits.com?content folder/tribalpolicy.pdf.
3. Basu SK. A health profile of tribal India. Health Millions. 1994 Apr 1;2(2):12-4.
4. WHO global tuberculosis report; 2016. Available at: http://www.who.int/tb/publications/global_report/en/.
5. 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.
6. WHO. Tuberculosis Control in South East Asia Region, Regional Report; 2016.
7. Arora VK, Gupta R. Directly observed treatment for tuberculosis. Indian J Paedtr. 2003;70:885-9.
8. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician. 2005 Nov 1;72(9):1761-8.
9. Lawn SD, Mwaba P, Bates M, Piatek A, Alexander H, Marais BJ, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. Lancet Infectious Dis. 2013 Apr 1;13(4):349-61.
10. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, et al. Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis for India. Indian J Med Res. 2017 Apr;145(4):448.
11. Pandit S, Dey A, Chaudhuri AD, Saha M, Sengupta A, Kundu S, et al. Five-years experiences of the revised national tuberculosis control programme in northern part of Kolkata, India. Lung India: official organ of Indian Chest Society. 2009 Oct;26(4):109.
12. Gonzalez OY, Adams G, Teeter LD, Bui TT, Musser JM, Graviss EA. Extra-pulmonary manifestations in a large metropolitan area with a low incidence of tuberculosis. Int J Tuberculosis Lung Dis. 2003 Dec 1;7(12):1178-85.
13. Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob. 2015 Dec;14(1):34.
14. Tahir M, Sharma SK, Rohrberg DS, Gupta D, Singh UB, Sinha PK. DOTS at a tertiary care center in northern India: successes, challenges and the next steps in tuberculosis control. Indian J Med Res. 2006 May 1;123(5):702.
15. Maltezou HC, Spyridis P, Kafetzis DA. Extrapulmonary tuberculosis in children. Arch Dis Child. 2000;83:342-6.
16. Prakasha SR, Suresh G, D'sa IP, Shetty SS, Kumar SG. Mapping the pattern and trends of extrapulmonary tuberculosis. J Global Infect Dis. 2013 Apr;5(2):54.

17. Mavila R, Kottarath M, Nair S, Thaha MM. Site predilection of extrapulmonary tuberculosis: study from a tertiary care centre. Int J Res Med Sci. 2017 Jan 16;3(11):3386-90.
18. Ilgazli A, Boyaci H, Basyigit İ, Yildiz F. Extrapulmonary tuberculosis: clinical and epidemiologic spectrum of 636 cases. Arch Med Res. 2004 Sep 10;35(5):435-41.
19. Berger HW, Mejia E. Tuberculosis Pleurisy. Chest. 1973;63(1):88-92.
20. Scharer L, McClement JH. Isolation of tubercle bacilli from needle biopsy specimens of parietal pleura. Am Rev Respir Dis. 1968;97(3):466-8.
21. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Resp Med. 2015 Jun 1;3(6):451-61.
22. Lawn SD, Zumla AI. Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF assay. Expert Rev Anti Infect Ther. 2012;10(6):631-5.

Cite this article as: Rao CM, Thakur B, Thakur S, Dash DP. Pattern of extra pulmonary tuberculosis among urban population with special reference to CBNAAT as a diagnostic tool: a retrospective study at a tertiary care hospital of Odisha, India. Int J Res Med Sci 2018;6:3375-80.