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

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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. The impact of TB is higher with greater involvement of extra pulmonary organs in this vulnerable population.

Globally around 10.4 million people contract tuberculosis. Of these in India there were an estimated 2.8 million new cases and 0.48 million deaths due to TB in 2015. Incidence rate of TB is 167(156-179)/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.

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. 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. Once the diagnosis has been considered, confirmation can be difficult, with sample collection from deep-seated tissues being challenging and the disease typically being paucibacillary.

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. This diagnostic facility is available at the Regional Medical Research Centre (ICMR), Bhubaneswar. Both respiratory and non-respiratory specimens are accepted for CBNAAT study. Kaling 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 CBNAAT 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              | 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 extrapulmonary 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| 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  | 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%)| 10 (5.0%)| 3 (1.5%)| 1 (0.5%)| 195 |
| Female  | 97 (60.2%)| 36 (22.4%)| 9 (5.6%)| 2 (1.2%)| 12 (7.4%)| 10 (6.0%)| 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    | 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 | Sensitivity=100% | Specificity=87.5% |
|------------------------|------------------------|-------|------------------|------------------|
| CB NAAT Positive       | 7                      | 7     | 14               |                  |
| CB NAAT Negative       | 0                      | 49    | 49               |                  |
| Total                  | 7                      | 56    | 63               |                  |

Table 7: Treatment outcome 2013-2017.

|       | Total | Completed treatment | Default | Death |
|-------|-------|----------------------|---------|-------|
| CAT I | 422   | 415                  | 7       | 3     |
| 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), Aysef 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 assessment 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 Ilgazi 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.\textsuperscript{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 Xpert. Xpert pooled sensitivity was consistently 98.7% against CRS across different sample types.\textsuperscript{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).\textsuperscript{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. Lymph 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.

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