Original Research Article

Study of extrapulmonary tuberculosis in tertiary care hospital children with reference to cartridge based nucleic acid amplification test

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ABSTRACT

Background: Tuberculosis is an infectious disease caused by the mycobacterium tuberculosis which typically involves lung but can affect other sites called extrapulmonary tuberculosis (EPTB). In EPTB lymph node tuberculosis is most common and most severe is tuberculous meningitis. Cartridge based nucleic acid amplification test (CBNAAT) have high sensitivity and perform both respiratory and non-respiratory specimens. The aim of this retrospective study is to find out the proportion of extra pulmonary tuberculosis in hospitalized patients and determine the association of CBNAAT in diagnosis of EPTB and Rifampicin resistance.

Methods: This is the retrospective observational study done at Civil Hospital Ahmedabad in between October 2017 to October 2019 among the admitted patients age 1 month to 12 years diagnosed cases of EPTB according to RNTCP guidelines. Data collection done by medical records as indoor case sheets and investigation data from laboratory department.

Results: Incidence of EPTB among the hospitalized children is 1.95% and among total tuberculosis patients is 42.48%. Among 191 suspected EPTB cases 59 confirmed indicate sensitivity of 37.3% and no false positive cases indicate 100% positive predictive value. Sensitivity of CBNAAT was highest in gastric aspirate followed by CSF in present study.

Conclusions: Tuberculosis is more common in male child less than 5-year-old with frequent risk factor is rural residential area, lower socioeconomic class and contact with active cases. In my study CNS tuberculosis is most common. In my study mortality is higher among 1-to-5-year age group with co morbid conditions are SAM and septicemia.

Keywords: EPTB, CBNAAT, RNTCP, TB lymphadenitis, CNS tuberculosis

INTRODUCTION

Global tuberculosis (TB) 2018 Report suggest that in India average 2.2 lakh children become ill with TB each year (22% Of global TB burden) with slightly higher burden among males. Pulmonary TB is the most common form in Tuberculosis in children but the extra pulmonary TB forms a larger proportion than in adults.¹

Tuberculosis is an infectious disease which is caused by the Mycobacterium tuberculosis which typically involves the lung (Pulmonary TB) but can affect other sites called

extra pulmonary tuberculosis. In extra pulmonary tuberculosis lymph node tuberculosis is most common in form of EPTB and most severe form in EPTB is tuberculous meningitis (TBM). Worldwide extra pulmonary tuberculosis accounts for 25% of all TB cases and even higher percentage in HIV infected individuals and children.²

The major challenge in diagnosis of EPTB is that frequently atypical presentation, low bacillary load, lack of access to health care because live in vulnerable and poor community.

The conventional Mycobacterium tuberculosis detection technique based on microscopic examination of acid-fast bacilli is relatively insensitive. CBNAAT/Gene Expert MTB/RIF have been the game changer as they have far high sensitivity than smear almost reaches to culture and perform both respiratory and non-respiratory specimen. CBNAAT is real time PCR technique diagnosis of TB and detection of rifampicin resistance conferring mutation within 2 hours.

CBNAAT sensitivity and specificity in sputum is around 98% and 99% for smear positive patient and 72% for smear negative culture positive patient and for GA have been 68% and 99% respectively.^{3,4}

Aims and objectives

To study the incidence of extra pulmonary tuberculosis in hospitalized patients to determine the association of CBNAAT in diagnosis extra pulmonary tuberculosis and rifampicin resistance.

METHODS

The study was a retrospective, conducted at tertiary level hospital at pediatrics department Civil Hospital Ahmedabad Gujarat in between October 2017 to October 2019. Out of 191 patients 158 patients met the criteria of RNTCP CRS (composite reference standard) which include smear microscopy, clinical finding at time of presentation and investigation. Study included patients admitted age group from 1 month to 12 years with suspected as presumptive case of extra pulmonary tuberculosis according to RNTCP GUIDELINES were

included and diagnosed outside private and government sector.

Study excluded patients take treatment OPD based and isolated pulmonary tuberculosis.

Data collection done by detailed history with complete clinical and physical examination. Family history with close contact and BCG vaccination and socioeconomic status of children classified according to modified Kuppaswamy Classification. The nutritional status assessed and classified according to IAP classification and BMI according to age.

Software used for data analysis was Microsoft Excel. RNTCP guideline applied for diagnosed extra pulmonary tuberculosis. Relevant investigation done with special reference regarding CBNAAT was done. All children tested for HIV.

All patient treated as per RNTCP Guideline 2019. In suspected extra pulmonary tuberculosis patient sample collected under aseptic precaution and sent to examine for Gene Expert at RNTCP lab at state TB Division Centre Ahmedabad.

RESULTS

In my study total number of patients diagnosed with TB among total number of patients admitted during the study period (10468) were 481 suggestive of incidence is 4.59%, in which patients detected with EPTB were only 191 (1.95%).

Table 1: Associated risk factors.

Risk factors	Present study (n=191)		Virani et al (2008) (n=100) ⁵	Israni et al (2015) (N=50) ⁶
		Cases %		
BCG vaccination	Vaccinated	135 70.7	72%	55%
	Unvaccinated	56 29.3	28%	45%
Positive contact history	Present	85 44.5	36%	50%
Previous history of tuberculosis	Present	21 10.8	21%	
Socioeconomic status	Upper class	15 7.8		
	Middle class	58 30.3		
	Lower class	118 61.7	90%	74%
Residential area	Rural	127 66.4	60%	
	Urban slum	49 25.07		
	Urban	15 7.8	33%	
Nutritional status (<5 year)	Normal	36 25.8	Vimlesh et al (2003)	
	PEM Grade 1	21 15.1	50.4%	
	PEM Grade 2	19 13.6		
	PEM Grade 3	25 17.9	33.4%	
	PEM Grade 4	38 27.3		
>5 year)	Normal	6 11.5	53.4%	
	Moderate undernutrition	10 19.2		
	Severe undernutrition	36 69.2		

Table 2: Distribution of childhood EPTB.

Site	Present study (n=191)		Virani et al 2008 ⁵	Vimlesh et al AIIMS (2003) ⁸
	Cases	%		
CNS tuberculosis	85	44.4	46%	4%
Pleural TB	29	15.1	12%	
Abdominal tuberculosis	26	13.9	10%	
Disseminated tuberculosis	26	13.9	21%	8%
Cervical lymphadenitis	15	7.8	7%	78%
Pott's spine	03	1.5		
TB skin (scrofuloderma)	02	1.04		
TB osteomyelitis	04	2.09	4%	4%
Genitourinary tuberculosis	01	0.5		

Global TB report 2018 reports that in India, Annual incidence of Tuberculosis in 199 per 1 lakh population which results in 2.2 lakh cases every year (22% of global

TB burden).¹ 15-20% these cases are of EPTB. Approximately 10% the total cases reported to RNTCP are from children <14 years of age.⁴

Anil et al and Virani et al have also observed similar risk factors comparable with present study.^{5,6}

ICMR survey 2005 states prevalence of disease is equal in both rural and urban whereas Chadha et al observed TB infection rate is higher in urban areas (2.2%) than in rural areas (1.3%).⁷

CNS tuberculosis was the most common form of EPTB observed in 44.4%. In study of Sheth et al, TB lymphadenitis (78%) was the most common form of EPTB.⁸

Lower sensitivity could be due to either small sample, inadequate sample collection, improper transport and delay in processing.

Out of total 191 patients, 158 were CRS positive, among which 59 were CBNAAT positive (true positive cases), 99 were CBNAAT negative (false negative cases). 33 patients does not match CRS criteria and were also CBNAAT negative (Empirically AKT started) (true negative).

Table 3: Analysis of CBNAAT results in EPTB samples.

Tubercular cases	Positive		Tortilo et al 2012 ⁹ (%)	Avashia et al 2016 ¹⁰ (%)
	Cases	%		
Gastric aspirate(n=161)	53	32.97	97.3	-
Sputum(n=45)	8	17.75	88	-
CSF(n=85)	26	30.5	85.7	33.3
Ascitic fluid(n=15)	2	13.3	50	20
Pleural fluid(n=29)	3	11.5	44.4	23.3
Lymph node(n=20)	3	15	88.3	54.2
Total sample 355	95	26.7	81.3	37

Table 4: Calculation of indices for CBNAAT.

	CRS +ve	CRS -ve	Total
CBNAAT +ve	59	-	59
CBNAAT -ve	99	33	132
Total	158	33	191

To reduce the percentage of true negative cases ideally it is recommended to perform culture studies in all CBNAAT negative cases.

Lower sensitivity could be due to either small sample size, inadequate sample collection, improper transport and delay in processing.

Sensitivity and specificity of CBNAAT in sputum sample is around 98% and 99% in smear positive whereas both are around 72% in smear negative but culture positive patients. Sensitivity and specificity have been 68% and 99% respectively (RNTCP pediatric guidelines 2019).

Currently, WHO estimated incidence of Rifampicin resistance and MDR TB in INDIA is estimated to be around 147000. This translates to be around 11 patients per 100000 population annually as per the Global TB Report, WHO 2018.¹

According to Global TB report 2018 In India TB mortality ranges from 30-35 /1 lakh population and children's account for 10-15% among cases. The TB

mortality rate is falling at about 3% per year with the overall reduction of 42% in the period from 2000-2017.¹

Table 5: Comparison of CBNAAT indices with other studies.

Study	Sensitivity (%)	Specificity (%)
Present study	37.3	100
Hilleman et al ¹¹	77.3	98.2
Ahmad et al ¹²	37	
Avaisha et al ¹⁰	37	
Tortoli et al ⁹	81.3	99.8

Table 6: Comparative analysis of CBNAAT versus smear results.

Specimen	Smear (%)	CBNAAT (%)
Gastric aspirate	6.2	32.9
Sputum	10	17.75
CSF	4.5	30.5
Pleural fluid	2	11.5
Ascitic fluid	-	13.5
Pus (lymph node)	3.8	15

Table 7: Outcome in patients.

Outcome	Cases (n=191)	%	Virani et al (2008) (%)	Gosai et al (2011) (%)
Discharged	134	70.1	66	74
LAMA	19	9.9	13	12
Expiry	38	19.8	20	12

Table 8: Analysis of MDR TB patients.

MDR patients profile	Cases (n=8)
Prevalence among EPTB	8 (4.1%)
HIV co-infection	2
SAM	3
Defaulter	3
Treatment failure	2
Contact with MDR TB known case	6
CBNAAT positive	3
Mortality	3 (37.5%)

According to Global TB report 2018 estimated burden of MDR/RR cases were 5.58 lakh in world and 1.35 lakh in India.

Among cases of MDR TB 8.5% were estimated to have XDR TB. Three countries accounted for almost half of

the world cases of MDR/RR TB: India (24%), China (13%) and Russian federation (10%) (Global TB report 2019).

Figure 1: Calculation for indices for CBNAAT.

Figure 2: Rifampicin resistance detected by CBNAAT.

DISCUSSION

Incidence of TB among hospitalized children was 4.59%. Incidence of EPTB was 1.95% which contribute up to 39.7% all pediatric TB patients. Male to female ratio is 1.27. Among them 72.7% of children were less than 5 year of age. In various study, Sheth et al and Virani et al also has male predominant.^{8,5}

Rural residential area (66.4%), lower socio-economic class (61.7%) and contact with active TB (44.5%) were the most frequent risk factor. Severe nutritional anemia (43.9%) and severe acute malnutrition (30.3%) were the most common co morbid condition. Israni et al and Virani et al have also observed similar risk factors comparable with present study.^{5,6} Fever is most common constitutional symptom (80.1%). Pallor (48.6%) and generalised lymphadenopathy (30.8%) were the most common generalised signs. Also in comparative study, fever is common symptoms (72.3% in Israni et al and 97% in Virani et al) followed by cough cold and weight loss.^{5,6}

CNS TB is most common form of EPTB observed in this study (44.4%). In Vimlesh et al, cervical lymphadenopathy (78%) is common in EPTB.⁸

Out of 191 patients 25.1% show positive CXR finding in form of effusion (16.2%) followed by consolidation (16.2%). In neuro-imaging hydrocephalus was most common abnormality (74%). MT positive in 28.2%.

Overall positivity of ZN stain in various body fluid around 4% only. Sensitivity of CBNAAT was highest in Gastric aspirate (32.97%) followed by CSF (30.5%) in present study. Sensitivity of gene expert for plrural fluid, ascitic fluid and lymph node is 11.5%,13.3% and 15% respectively. Among 158 EPTB cases 59 were CBNAAT confirmed indicate sensitivity of 37.3% and no false positive cases indicates 100% positive predictive value. Positivity of CBNAAT was significantly higher as compared to smear examination in all specimen. Table 5 suggest comparison of various study with CBNAAT indices.

Rifampicin resistance was 5%. Adverse effect of anti-tubercular drugs were seen in 25.6%. Similar as in Hillemann et al study rifampicin resistance was noted in 5.79% and in Avashia et al was 5.40%.^{10,11} Acute life-threatening complication like cardiac temponade and intestinal perforation were observed.

Overall mortality rate of EPTB in present study was 19.8% with highest among CNS TB (32.9%) followed by disseminated TB (26.9%), pleural TB (7.6%) and abdominal Koch (3.6%).

In present study we are not estimated total incidence of EPTB as OPD based treated and other than study hospital treated patients are not included. Also, in present study excluded the pulmonary tuberculosis cases so that CBNAAT sensitivity and specificity and also rifampicin resistance detection by Gene Xpert cannot be estimated overall.

CONCLUSION

Tuberculosis is more common in male child less than 5-year-old with most frequent high-risk factor is rural residential area, lower socioeconomic class and contact with active TB patient. In general TB Lymphadenitis is most common type of EPTB but in my study is CNS tuberculosis is most common. In my study mortality is higher among 1-to-5-year age group with most co morbid condition are SAM and septicemia. Rifampicin resistance observed was 5%.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. WHO global tuberculosis report. 2018. Available at: <https://apps.who.int/iris/handle/10665/274453>. Last accessed at 04 July 2021.
2. Central TB Division. Tuberculosis India 2019. Annual report of the Revision National Tuberculosis Control Programme, Directorate of general health services. Ministry of Health and Family Welfare, gov of India 2012. <https://tbcindia.gov.in/index1.php?page=1&ipp=All&lang=1&level=1&sublinkid=4160&lid=2807>. Last accessed at 04 July 2021.
3. Draft updated IAP RNTCP Ped Tuberculosis Guideline 2019. Available at: <http://tbcindia.gov.in>. Accessed on 19 July 2021.
4. Director general health services. Department of tuberculosis (NTP) DGHS, MOHFW, New Delhi.
5. Virani T, Shukla S. Clinico radiological profile and operationalisation of childhood tuberculosis dissertation, Vadodara. 2008. https://apps.who.int/iris/bitstream/handle/10665/112472/9789241506335_eng.pdf;jsessionid=7AB23A85B2B65B79B6705D6ECFF47A08?sequence=1. Last accessed at 04 July 2021.
6. Israni A. Tuberculus meningitis in children (Tubercular meningitis in children: clinical, pathological and radiological profile and factors associated with mortality). Journal Of Neuroscience In Rural Practice. Available at: https://www.researchgate.net/publication/301740369_Tubercular_meningitis_in_children_Clinical_pathological_and_radiological_profile_and_factors_associated_with_mortality. Last accessed at 04 July 2021.
7. Chadha VK, Jagannatha PS. Average annual risk of tuberculosis infection in india Int. J Tuberc Lung Dis. 2005;9:116-8.
8. Sheth V, Kabra SK. Essential of tuberculosis in children, 3rd edition. 150-1.
9. Tortoli EC, Russo. Clinical validation of Xpert MTB /RIF for diagnosis of extra pulmonary tuberculosis. Int J Inf Dis. 2020;95:15-21.
10. Avishia S, Bansal D, Agrawal AK. Comparision of conventional methods with Gene XpertMTB/RIF for Rapid detection of mycobacterium tuberculosis and rifampicin resistance in extra pulmonary sample. Int j Med Res. 2016;4(2):181-5.
11. Hillemann D. Rapid detection of mycobacterium tuberculosis and rifampicin resistance in extra pulmonary sample using Gene Expert MTB/RIF. Syteme J Clin Microbial. 2011;49(4):1202-5.
12. Ahmad NS, Khan S. Rapid detection of mycobacterium tuberculosis and rifampicin resistance in extra pulmonary samples using Gene XpertMTB/RIF. ISOR Journal of Dental and Medical science. 2014;13(11):2279-861.

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