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(RESEARCH ARTICLE)

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Clinical spectrum of pediatric tuberculosis and early diagnosis by clinical, radiological, and CBNAAT in a Tertiary Care Teaching Hospital in South India

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Abstract

Background: In India, an estimated 220,000 children contract tuberculosis (TB) annually, yet the absence of a gold standard test hinders effective diagnosis and reporting of childhood TB.

Objective: This study aimed to analyse the clinical profile of childhood tuberculosis, utilizing relevant laboratory investigations for early diagnosis.

Methods: A cross-sectional observational study was conducted at a tertiary care hospital in South India from October 2019 to October 2021. Children under 18 with tuberculosis were included. Data on demographics, symptoms, family TB history, nutritional status, and clinical findings were collected. Laboratory tests included complete blood count, ESR, Mantoux test, chest X-rays, and sputum analyses for acid-fast bacilli (AFB).

Results: Among 54 children, the most common age group was over 10 years (51.3%), with a male preponderance (53.3%). Pulmonary TB was diagnosed in 44.4% of cases, while 55.5% had extrapulmonary TB, predominantly pleural (40%). Fever (60.5%) and cough (42.7%) were the most common symptoms. The Mantoux test was reactive in 40.7% of patients, particularly among the undernourished. Chest X-rays indicated TB in 93.25% of pulmonary cases, while CBNAAT showed positive results in 10 cases, with a sensitivity of 18.8% and specificity of 81.25%.

Conclusions: Diagnosing childhood TB remains complex, relying on symptom evaluation, clinical history, and laboratory tests. Despite advances in diagnostic methods, negative CBNAAT results do not exclude TB, highlighting the need for thorough clinical assessment and investigation.

Keywords: Pediatrics; Clinical profile; Tuberculosis; CBNAAT

1. Introduction

Tuberculosis is one of the most widespread infections and affects almost one-third of the world's population. It is the first infectious disease to be declared a global health emergency.[1] Global TB report 2018 reports that in India, an estimated 2.2 lakh children become ill with tuberculosis (TB) each year (22% of global TB burden), with a slightly higher burden among males.[1] Pulmonary TB is the most common form in children but the extra-pulmonary TB forms a larger proportion of cases than in adults. It is also known that about 10% of the cases reported to RNTCP are from children under 14 years of age.

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In children with presumptive pediatric TB, every attempt must be made to microbiologically prove diagnosis through examination of appropriate respiratory/non-respiratory specimens with quality assure d diagnostic tests. The program is usually the adult oriented and hence the diagnostic strategies of the children and adults antithesis to each other i.e. smear to radiology versus radiology to smear. Lack of standard definitions, absence of simple/reliable diagnostic test and more extra pulmonary TB cases add to lack of data on pediatric TB. There is also gross under estimation of magnitude of the problem[2].

The major challenge of childhood tuberculosis is establishing an accurate and early diagnosis, as children are rarely smear positive.[2] 95% of cases in children less than 12 years are smear negative. Smear positive cases in <14 years accounted 0.6 to 3.6% of reported cases.[3] Collecting an adequate sample for microbiological diagnosis also presents a significant challenge particularly for small children who cannot provide a good sputum specimen.[2] Early diagnosis and successful treatment is the most effective means to protect children from infection with tuberculosis.

Cartridge based nucleic acid amplification test (CB NAAT - Gene X-pert) is a new test for tuberculosis. It uses real time polymerase chain reaction to detect mycobacterium tuberculosis and rifampicin resistance in samples in only 2 hours.[4] The gene X-pert integrates sample processing, nucleic acid amplification and detection of target sequence. The reactions take place in a single use cartridge. The PCR target, an 81 base pair region of rpoB gene, contains a signature sequence for identification of tuberculosis and involves the locus where majority of mutations associated with rifampicin resistance occur.[5] It has high sensitivity and specificity, and is also easy and safe to perform.[11]

Objectives

- To study the clinical spectrum and disease burden of pediatric tuberculosis in a tertiary care teaching hospital in south India
- Early diagnosis by clinical manifestations, radiological and special emphasis of sensitivity of CBNAAT.

2. Materials and methods

- **Source of Data:** Tertiary care teaching hospital in south India
- **Study Design:** Cross-sectional Observational Study
- **Study period:** 2 years (October 2019 – November 2021)
- **Sample size:** 54

2.1. Method of Collection of Data (Including Sampling Procedures if any)

Ethics approval for conducting the study was obtained from the institutional ethics committee and informed consent was taken from parents of all children included in the study. Children between the age group of 6 months to 18 years admitted with presumptive tuberculosis as per criteria of Pediatric Revised National Tuberculosis Control Program 2019, in pediatric ward in a tertiary care teaching hospital in south India formed the study group. These children's detailed history and examination findings were recorded in a predefined, structured, standard proforma. Demographic details, presenting symptoms, family history of TB contact, nutritional status and clinical examination findings were documented. Complete blood count, ESR, Mantoux test, chest X-ray and sputum analyses for AFB were done for all patients. Either sputum or resting gastric juice was taken for detecting acid fast bacilli in relevant patients for CBNAAT

2.1.1. Inclusion Criteria

Children between the age group of 6 months to 18 years admitted with symptoms suggestive of presumptive tuberculosis (pulmonary and / extra pulmonary) as per criteria of Revised National Tuberculosis Control program guidelines 2019

2.1.2. Exclusion criteria:

Children who are presently on anti-tubercular therapy and who have received the same in the past.

3. Results

A total of 54 children, diagnosed with tuberculosis in our hospital during the study period of 2 years and satisfying the inclusion and exclusion criteria were recruited for the study. Among the study population, children between 1-5 years of age 13 (24.15%), between 6-10 years were 13 (24.1%) and more than 10 years were 28 (51.6%). There were an

increased number of childhood tuberculosis patients in more than 10 years of age. The total number of males were 29 (53.73%) and females were 25 (46.29%) and male preponderance was seen in all age groups. (Table1)

Table 1 Socio demographic profile of TB cases

Demographic profile	Frequency	Percent
Sex		
Male	29	53.7
Female	25	46.4
Age group(years)		
1-5	13	24.1
6-10	13	24.1
11-15	17	31.5
16-18	11	20.4
Economic class		
Lower class	14	25.9
Lower middle	15	27.8
Upper class	3	5.6
Upper lower	12	22.2
Upper middle	10	18.5
Contact history		
Present	28	51.9
Absent	26	48.1
BCG vaccination status		
Present	49	90.7

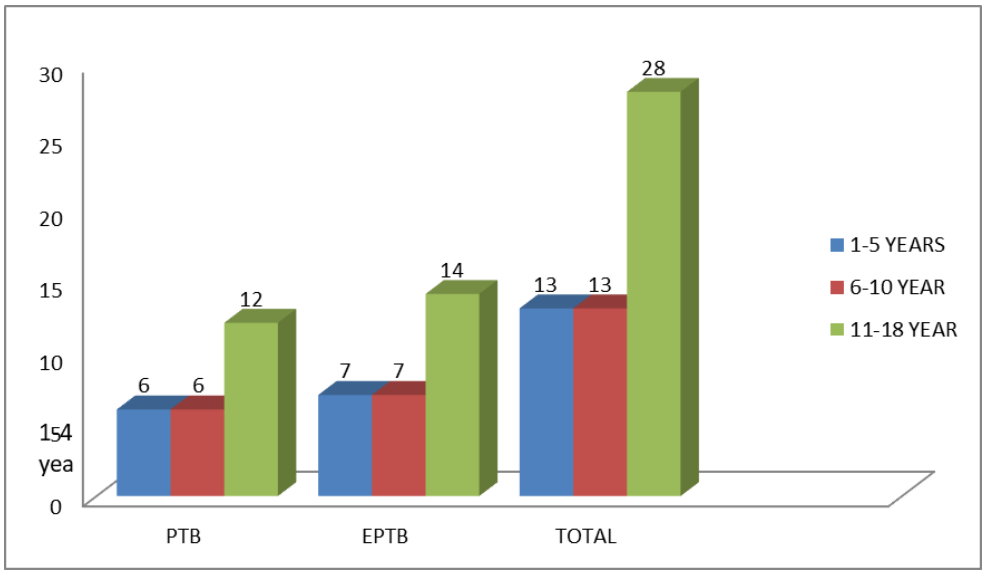

Figure 1 Age wise distribution of pulmonary and extrapulmonary TB cases

The predominant type of diagnosis was pulmonary tuberculosis in 24 (44.4%) patients, followed by extra pulmonary in 30(55.5) and disseminated type was noticed in 1 case (1.85%). Among the 30 cases with extra pulmonary TB, pleural TB (n=12, 40%) was the most common manifestation. Central nervous system (n=10, 33.3%), lymph node TB (n=4, 13.3%) and abdominal TB (n=4 7.4%).

Table 2 Distribution of different forms of TB in the study

Pediatric tuberculosis	Frequency	Percent
Pulmonary TB	24	44.4
Pleural TB	12	22.2
TB meningitis	10	18.5
Lymph node TB	4	7.4
Abdominal TB	4	7.4
Disseminated TB	1	1.9

Overall, fever (n=50, 60.5%) was the predominant symptom noted, followed by cough (n=53, 42.7%). Whereas, lymph node swelling in 4 patients was the predominant symptom in extra pulmonary form of tuberculosis patients. There were an increased number of undernourished patients in pulmonary TB group and BCG scar was seen in the majority of patients (n=47). There were 4 HIV positive patients (7.4%), belonging to the pulmonary group. Around 20 (37%) pulmonary tuberculosis patients had a positive contact history with known tuberculosis patients. Patients diagnosed with extra pulmonary TB (n=6, 40.6%) and disseminated type (n=1, 20%) had a positive contact history.

Erythrocyte sedimentation rate (ESR) was done in all the patients in the study. High ESR (>20mm) was noted in 13 (24.07%) patients in pulmonary group and 4 (7.40%) patients in extra pulmonary group.

Table 3 Clinical signs and symptoms of TB cases

Signs and symptoms	Frequency	Percent
Fever	52	96.29
Cough	15	27.7
Loss of appetite and weight	52	96.3
Lymphadenopathy	18	33.3
Convulsions	8	14.8
Pain abdomen	3	5.55
Diarrhea	2	3.7
Right hemiplegia	1	1.9
Chest pain	2	3.7
Breathlessness	18	33.3

Overall, the Mantoux screening test was reactive in 22 (40.7%) patients and two-thirds of the undernourished children were Mantoux positive.

Either sputum or resting gastric juice was taken for detecting acid fast bacilli in relevant patients, and it was found to be positive in 4 (7.40.5%) patients in pulmonary group and 1 (1.9%) among disseminated TB patients.

Table 4 Distribution of investigations (high ESR, Mantoux positivity, AFB smear positivity, positive radiological findings and CBNAAT in pediatric TB in study

Tests	Frequency	Percent
ESR High Normal	7 47	13 47
Mantoux positive Negative	22 32	40.7% 59.2%
AFB smear positive Negative Not done	5 37 12	9.25% 68% 22.2%
Radiological findings Suggestive of TB CXR	 26	48.1%
CBNAAT Positive Negative	 10 44	 18.51% 81.48%
HIV Positive Negative Not done	 4 20 30	 16.6%

Chest radiograph findings suggestive of tuberculosis were noted in 93.25% pulmonary tuberculosis patients and all the disseminated tuberculosis patients (Figure II). Non-homogenous opacities (patchy infiltrations) in lung fields were the most common finding.

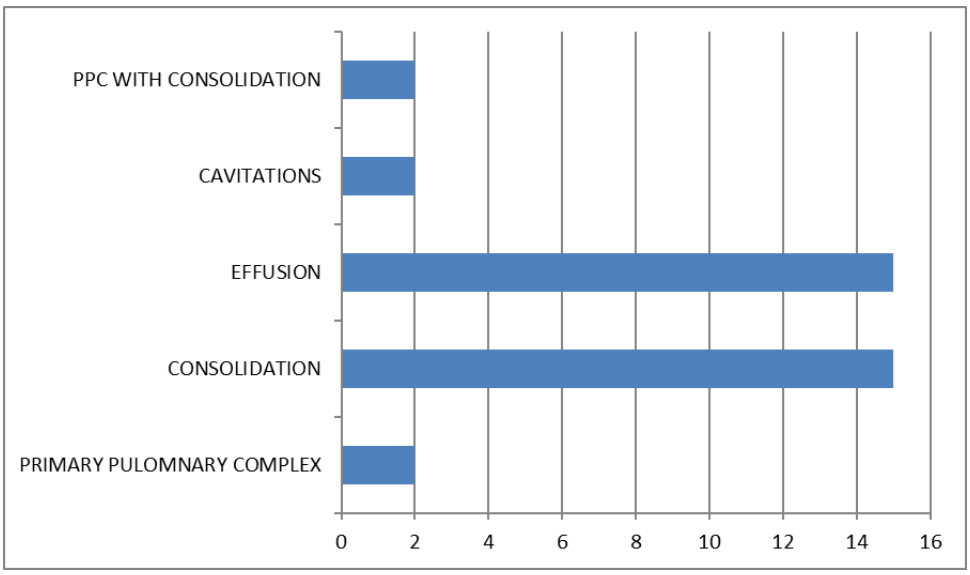

Figure 2 Radiological findings of chest X-ray of positive cases in study

Out of 54 cases in TB group X-pert MTB showed positive results in 10 cases.

The sensitivity of X-pert was 18.8% compared to clinical diagnosis of TB and specificity was 81.25%. The diagnostic significance of CBNAAT in various TB has been given in table V.

Table 5 Diagnostic significance of CBNAAT in various types of TB

Type of TB	CBNAAT		
	Positive	Negative	Total
Pulmonary TB	7 (70%)	17(38.6%)	24(44.4%)
TB meningitis	0 (0%)	10(22.7%)	10(18.5%)
Pleural TB	2 (20%)	10(22.7%)	12(22.7%)
Abdominal TB	1 (10%)	3(6.7%)	4(5.6%)
Lymph node TB	0		4(7.4%)

4. Discussion

There was a higher prevalence of tuberculosis in the age group of more than ten years than younger kids in the present study. This may be due to the inclusion of children till 18 years of age. This finding was similar to the study conducted on childhood tuberculosis by Shrestha S et al, in Nepal.[2]

Pulmonary tuberculosis was the more common form of tuberculosis in present study than extra pulmonary and disseminated TB. This was the similar finding in a study conducted by Goyal A et al[6], on childhood tuberculosis. Pleural TB and central nervous system TB were the predominant manifestation among extra pulmonary forms of tuberculosis in the present study.

Cough and sputum production were the most common symptoms noticed in pulmonary tuberculosis patients followed by fever. Pama CP et al[7], in their study of tuberculosis, found that the frequent symptoms were fever (86.6%), cough (76.1%), malnutrition (52.3%), weight loss (50.7%), anorexia (44.8%), breathing difficulty (18%) and convulsions. (8%)

Lymph node swelling (33%) was the predominant symptom in extra pulmonary form of tuberculosis patients.

About 65.5% of pulmonary TB children were undernourished in the present study.

Swaminathan S et al, documented 62% of TB patients with grade III and IV malnutrition in their study.[3] Majority of patients had BCG scar in the present study (87%).

Mantoux reactivity was noted in (33.3%) children with pulmonary TB (30.7%), 75% of extra pulmonary TB, Sreeramareddy CT et al[8], in their study on tuberculosis, had a Mantoux positivity of 66% in pulmonary group with higher Mantoux positivity of 71% in extra pulmonary form of tuberculosis.[8]

Most common chest X-ray finding was pleural effusion in 15 cases (57%) consolidation in 11 (42%) followed by non-specific finding consolidation finding (4), hazy densities (6) and cavitations. (2%)

Microbiological confirmation is the gold standard for the diagnosis of TB. It also helps identify drug-resistant TB. Microbiological confirmation is not always possible in children due to the pauci-bacillary nature of pediatric TB[1] and difficulty in acquiring the sample. However, we were able to make microbiological confirmation by Gene X-pert in our study was positive in 10 cases (18.5%), 7 were of PTB patients (70%) compared to (30%) of patients of EPTB. Only one PTB patient was found to be rifampicin resistant in our study; the culture and sensitivity detected resistance to both isoniazid and rifampicin. The development of nucleic acid amplification tests (NAATs) holds promise. However, although several studies on diagnostic accuracy of (commercial) NAATs in adults were published were considerably heterogeneous, very few data are available on children.[11]

In December 2010, the X-pert MTB/RIF assay the X-pert was evaluated in clinical trials in adults, and most recently also in children with suspected tuberculosis, and showed good sensitivity and specificity in smear-positive and culture-positive and reasonable accuracy in smear-negative but culture-positive sputum samples[13].

Looking at these data, as well as the excellent technical characteristics, in our study the sensitivity of CBNAAT was 18.8%, and specificity 81.25% with CI (63.56-92.79).

The assay might be considered a promising diagnostic test in childhood tuberculosis that is simple enough to be used outside central laboratories.

Smear positive cases in present study was 9.3% with both pulmonary tuberculosis and in cases of TB lymphadenitis histopathological specimen was positive for Ziehl Neelsen staining.

5. Conclusion

Diagnosis of TB in children is often challenging this study reinforces that the diagnosis of childhood tuberculosis is based on the constellation of symptom evaluation, contact history, clinical examination, with relevant laboratory investigations. Although more rapid and sensitive laboratory testing, in molecular biology, immunology, and chromatography is being developed, a negative CBNAAT does not rule out TB. Hence this study supports that detailed history, clinical evaluation and active investigative workup has a major role in diagnosing childhood tuberculosis

Compliance with ethical standards

Acknowledgement

Each author has contributed towards patient care (establishing clinical diagnosis, planning investigations, management and follow-up) and writing the manuscript

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethics approval obtained from Institutional Ethics Committee.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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