Current Prevalence and Treatment Outcome of Paediatric Tuberculosis in a South Indian District - A 2 Year Retrospective Observational Study

Praveen Deen Kumar Namala[1], Praveena Basireddy[2]

[1]Department of Paediatrics, Government Medical College, Ananthapuramu, Andhra Pradesh, India.
[2]Department of Microbiology, Government Medical College, Ananthapuramu, Andhra Pradesh, India.

ABSTRACT

BACKGROUND

Knowledge about the diagnosis and the treatment outcome of paediatric tuberculosis is very much essential for functioning of tuberculosis (TB) control programs in most countries like India. The current study was done to determine the prevalence of paediatric tuberculosis, different modalities used for diagnosis, drug resistance pattern, HIV-TB co-infection rate and treatment outcome.

METHODS

A 2-year retrospective study was done among all registered paediatric tuberculosis cases aged 18 years and below, who were diagnosed during the period January 2018 to December 2019. Data was extracted from the files and was analysed.

RESULTS

The prevalence of paediatric tuberculosis was found to be 0.51 per 1000 population. The proportion of paediatric tuberculosis among total TB cases was 5.9 %. Among 14,596 total TB cases registered at District Tuberculosis Centre (DTC) Anantapuramu, 867 (5.9 %) were paediatric TB cases, with a mean age of 12.5 ± 5.6 years. 62 % of the cases were above 12 years of age. Males (47.4 %) and females (52.6 %) were almost equally distributed ($P > 0.05$). 343 (39.6 %) cases were microbiologically confirmed TB and 524 (60.4 %) cases were clinically diagnosed TB. Drug resistance was found in 47 (13.7 %) of the 343 microbiologically confirmed TB cases. Of the total 867 paediatric TB cases studied, pulmonary type (56 %) was predominant than extra pulmonary type (44 %) ($P < 0.05$). Human immunodeficiency virus (HIV) co infection was found in 24 (2.8 %) cases. 423 cases (65.5 %) successfully completed the treatment and 173 cases (26.8 %) were cured adding to a favourable outcome of 92.3 %. 3 (0.5 %) cases had treatment failure, 35 (5.4 %) were defaulters and 12 (1.8 %) cases died during the treatment, adding to a poor outcome of about 7.7 %.

CONCLUSIONS

Majority of the paediatric tuberculosis cases were diagnosed clinically rather than microbiological confirmation. Efforts should be made to further improve the availability and sensitivity of diagnostic methods of paediatric TB.

KEYWORDS

Paediatric Tuberculosis, Drug Resistant TB, HIV TB Co Infection

Corresponding Author:
Dr. Praveen Deen Kumar Namala,
11-1-359, Aravind Nagar,
Ananthapuramu - 515001,
Andhra Pradesh, India.
E-mail: basireddypraveena1@gmail.com

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BACKGROUND

The world health organization (WHO) estimates that, around 1 million children (< 15 yrs.) develop tuberculosis (TB) annually.[1] India is a highest TB burden country, where 25 % of global annual TB incidence occur.[2] In 2017 RNTCP has released a 'National strategic plan for tuberculosis 2017 - 2025' (NSP) for the control and elimination of TB in India by 2025. According to the NSP, TB elimination has been integrated into the four strategic pillars of Detect – Treat – Prevent – Build (DTPB).[3] At the start of 2020, the central government has renamed the RNTCP as the National Tuberculosis Elimination Program (NTEP).[4] Improving case detection, diagnostic accuracy and treatment availability are clearly critical to reduce TB-related child morbidity and mortality.[5] Smear microscopy for acid-fast bacilli may be available in primary-care settings, but it has limited diagnostic value in young children because of low yield.[6]

The WHO guidance on the approach to diagnosing TB in children includes 'bacteriological confirmation whenever possible'. The WHO classifies TB cases, including child TB cases, for notification and reporting either as 'microbiologically confirmed' (i.e, a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics such as cartridge-based nucleic acid amplification test (CBNAAT), True Nat or line probe assays) or as 'clinically diagnosed' which includes cases diagnosed and treated for TB on the basis of clinical signs, histopathological findings, radiological abnormalities and others like Mantoux test.[7] Newer rapid molecular techniques like CBNAAT, Tru Nat and line probe assays are a great breakthrough in modern science. Main two important advantages of these methods over conventional smear microscopy are they are more sensitive for diagnosis of both pulmonary and extra pulmonary and can detect drug resistance by analysing rpoB gene mutations in TB bacilli.[8]

The emergence and spread of resistant TB poses a serious threat to TB control. Acquisition of resistance rarely occurs in children due to the paucibacillary nature of their disease. Most resistance in children is due to primary transmission of a resistant organism. Resistance should be suspected if the primary case from whom the disease is contacted has known resistant TB or if the child shows initial improvement on anti-tubercular treatment (ATT) and then deteriorates or if there is no response to initial treatment. Rates of single drug, multi drug resistance (MDR) TB (resistance to both isoniazid and rifampicin) are rising in many parts of the world.[9]

HIV co-infection alters the pathogenesis of TB, increasing the risks of developing active TB in those with latent infection as well as in those newly exposed to TB.[10] World health organization (WHO) estimates that HIV prevalence among children with TB, in countries with moderate to high prevalence, ranges from 10 to 60 %.[11]

Objectives

1. To know the prevalence of paediatric tuberculosis
2. To study the different modalities used for diagnosis of paediatric tuberculosis
3. To assess the drug resistance pattern among paediatric tuberculosis patients
4. To know the paediatric HIV-TB coinfection rate
5. To estimate the treatment outcome among accessible study population.

METHODS

This is a retrospective observational study. All registered cases of TB aged 18 years and below at the management units in District Tuberculosis Centre, Ananthapuramu during the period from January 2018 to December 2019 were included.

Data Collection Tools

Data was collected from the TB records of the entire district at the District Tuberculosis Centre, Ananthapuramu. The records included the epidemiological, clinical, and microbiological data plus other essential data.

Data Analysis

Paediatric TB cases were classified based on the diagnostic modality used as microbiologically confirmed TB or as clinically diagnosed TB. Data was analysed by EXCEL and SPSS software. Chi-square test was used for categorical variables to evaluate the associations between dependent and independent variables. (e.g. age, sex, rural and urban residency, pulmonary or extra pulmonary, HIV reactive, HIV non-reactive, HIV status unknown). P value < 0.05 was taken as significant.

Specimen Processing Methods

All the studied samples were sent immediately to TB management units (TB unit) present in the district under control of District Tuberculosis Centre (DTC) which is under National Tuberculosis Elimination Programme. Samples were processed as central government policies for diagnosis of tuberculosis and also for diagnosis of drug resistance pattern in tubercle bacilli. Various methodologies have been following under DTC were as follows:

Smear Microscopy

1. Acid fast bacilli (AFB) stain - Two sputum samples were processed by AFB stain. One was on the spot sample and another was early morning sample. This method can detect 10000 bacilli/ml of sample.
2. Fluorescent stain - Fluorescent microscopy was 10 % more sensitive than AFB staining. Two sputum samples were processed by auramine O fluorescent stain method.

Gene Detection

WHO recommended Xpert *Mycobacterium tuberculosis* (MTB)/Rifampicin (RIF) rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having TB.

1. CB NAAT - Specimen was processed after purification and concentration using a cartridge based fully automated method. The CBNAAT is a semi-quantitative nested real-time polymerase chain reaction (PCR). Along with detection of bacilli, it can also detect rifampicin resistance.
2. Tru Nat - It is a chip based fully automated method which provides rapid results as CB NAAT. It analyses tubercle bacilli and drug resistance pattern after sample processing.
3. Line Probe Assay (LPA) - Line probe assay detects both tubercle bacilli and its drug resistance genes. Main advantage of this test is "detection of drug resistance genes in tubercle bacilli of both first line and second line antitubercular drugs. Here, according to drug resistance TB diagnostic algorithm which is under National Tuberculosis Elimination programme all suspicious TB samples were tested by CBNAAT.

Among CBNAAT results, if the organism was rifampicin resistant then particular sample was tested for second line anti tubercular drugs by LPA; if the organisms was rifampicin sensitive then particular sample was tested for first line antitubercular drugs by LPA.

Culture

MGIT Method (Mycobacteria Growth Indicator Tube method): Samples were processed immediately in liquid-based culture (Middlebrook 7H9 Broth base) which takes 4 - 8 weeks' time for either detection of bacilli or detection of drug resistance pattern.

Treatment Definitions

Cured

A patient treatment was started, after 5 months, her/his sputum (direct smear) changed from AFB - positive to AFB - negative.

Completed Treatment

A patient, who completed 6 months of Cat 1, clinically responded to treatment but with unknown bacteriologic status.

Treatment Failure

A patient whose treatment started 5 months or more, her/his sputum still remains positive or within the same time, changes from negative to positive again. Or the treatment of smear-negative cases in the beginning, but after two months of treatment, his sputum examination became positive.

Treatment Defaulter

A patient who is under treatment is said to be defaulted, if he/she stopped her/his treatment for 2 months or more.

Died

A patient expires for any reason during the course of treatment.

Favourable treatment outcome (cured and completed treatment) and poor outcome (failure, default and death) were measured after 6 months of the standard anti-TB regimen. For calculating treatment outcome, we excluded the patients who were under treatment (at the time of study) and lost to follow up. The remaining children with documented treatment outcomes were analysed.

RESULTS

Sl. No.	Various Factors		Number (%)	P value
1.	Age	< 5 yrs. 6 - 12 yrs. 13 - 18 yrs.	158 (18.2 %) 172 (19.8 %) 537 (62 %)	< 0.05 (S)
2.	Sex	Male Female	411 (47.4 %) 456 (52.6 %)	> 0.05 (NS)
3.	Region	Rural Urban	624 (72 %) 243 (28 %)	< 0.05 (S)
4.	Site of TB	Pulmonary Extra pulmonary	485 (56 %) 382 (44 %)	< 0.05 (S)
5.	HIV Status	HIV reactive HIV non-reactive HIV status unknown	24 (2.8 %) 776 (89.5 %) 67 (7.7 %)	< 0.05 (S)

Table 1. Distribution of Paediatric TB Cases Based on Various Factors (N = 867)

n: Number of cases, %: Percentage of cases, NS: Not significant (P > 0.05), S: Significant (P < 0.05)

	Diagnostic Modality	Number (%)
1.	**Microbiologically confirmed TB**	**343 (39.6 %)**
1a.	Microscopy (ZN & florescent staining)	127 (14.6 %)
1b.	Rapid molecular methods	
	CBNAAT	154 (17.8 %)
	Tru Nat	53 (6.1 %)
	Line probe assay	5 (0.6 %)
1c.	Culture	4 (0.5 %)
2.	**Clinically diagnosed TB**	**524 (60.4 %)**
2a.	Chest X-ray	156 (18 %)
2b.	Histopathology (FNAC, Lymph node biopsy)	257 (29.6 %)
2c.	Clinical signs	22 (2.5 %)
2d.	Others (Monteux test, USG, MRI, CT scan)	89 (10.3 %)
	Total	**867**

Table 2. Different Modalities Used for the Diagnosis of Paediatric TB (N = 867)

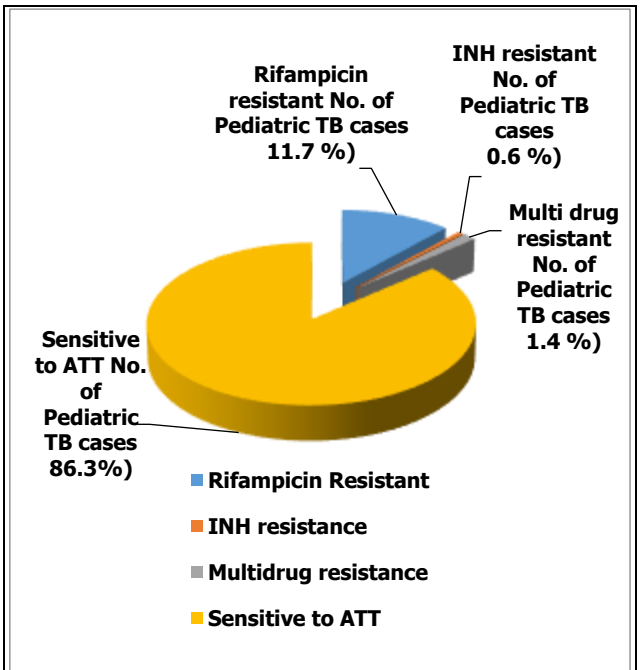

Figure 1. Drug Resistance Pattern in Paediatric TB

INH- Isoniazid, ATT- Anti Tubercular treatment

The prevalence of paediatric tuberculosis was found to be 0.51/1000 population. The proportion of paediatric tuberculosis among total TB cases was 5.9 %. Of the total 14,596 TB cases (including all age groups) registered at District Tuberculosis Centre, Ananthapuramu, 867 (5.9 %) cases were less than or equal to 18 years of age. Among 867 paediatric TB cases, majority of the cases i.e., 537 (62 %) cases were above 12 years. of age, 172 (19.8 %) cases were between 6 & 12 years and 158 (18.2 %) cases were less than 5 years of age with a mean age of 12.5 years with SD of 5.6 years. 411 (47.4 %) cases were males. 456 (52.6 %) cases were females and were equally distributed (P > 0.05).

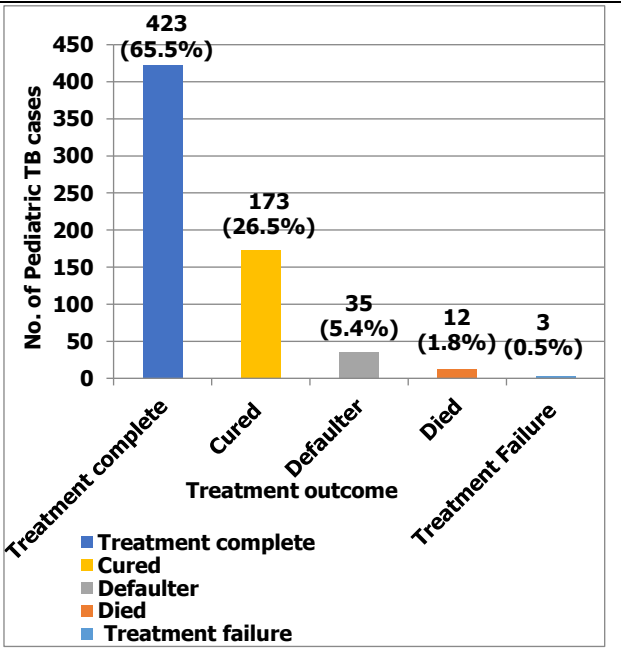

Figure 2. Treatment Outcome in Paediatric TB

Majority of the cases, 624 (72 %) are from rural areas and remaining 243 (28 %) cases were from urban areas (P < 0.05) as shown in Table 1. Of the total studied cases (N = 867), majority cases 485 (56 %) were diagnosed as pulmonary TB and 382 (44 %) cases were extra pulmonary (P < 0.05). HIV co infection was found in 24 (2.8 %) cases, 776 (89.5 %) cases were HIV non-reactive and in 67 (7.7 %) cases HIV status was unknown as shown in Table 1. On analysing the different diagnostic modalities used, 343 (39.6 %) cases were microbiologically confirmed TB and majority 524 (60.4 %) cases were clinically diagnosed TB as shown in Table 2. Out of the 343 microbiologically confirmed TB, drug resistance was found in 47 (13.7 %) cases of which 40 (11.7 %) cases showed Rifampicin resistance, 2 (0.6 %) cases showed INH resistant and 5 (1.4 %) showed multidrug resistance (Both resistant for Rifampicin and INH) as shown in Figure 1.

In our study, out of 867 paediatric TB cases, 26 (3 %) cases were lost to follow up and 195 cases were undergoing treatment, so we have excluded the above cases and the treatment outcome was calculated for the remaining 646 cases. Out of the remaining 646 cases, 423 (65.5 %) cases successfully completed the treatment, and 173 (26.8 %) cases were cured adding to a favourable outcome of 92.3 %. 3 (0.5 %) cases had treatment failure, 35 (5.4 %) cases were defaulters and 12 (1.8 %) cases died during the treatment adding to a poor outcome of about 7.7 % as shown in Figure 2.

DISCUSSION

In our study, the prevalence of paediatric tuberculosis was 0.51 per 1000 population. The proportion of paediatric tuberculosis among total TB cases was 5.9 %. In our study, older children more than 12 years represented the majority of paediatric TB cases (62 %), males and females were equally affected (P > 0.05). Tao N et al.[12] documented that out of 6283 children, 83.3 % were > 15 years of age, and no significant gender variation which is similar to our study. In contrast to this study, Ana Paula Ghussn Cano et al. reported 61.4 % were younger than 10 years of age. Raizada N et al.[13] reported that female children have two-fold of higher TB positivity when compared to male population. The variation depends on the demographic profile of the study population.

We identified significant difference between pulmonary TB (56 %) versus extra pulmonary TB (44 %) cases (P < 0.05) with predominant pulmonary type. In line with our study, Ana Paula Ghussn Cano et al.[14] reported 60.7 % of pulmonary type and 39.3 % were extra pulmonary type of tuberculosis. Raizada N et al.[13] also reported majority of the paediatric TB patients presented with pulmonary type comprising of 75.9 %. In contrast to our study Rebecca B et al.[15] reported extra pulmonary type (70.8 %) is predominant than pulmonary type (29.2 %). These variations may be attributed to disease prevalence as well as the availability of methods for early diagnosis and early notification.

2.8 % of the paediatric TB cases were HIV reactive in our study. Betsy et al.[15] from CMC Vellore, observed HIV TB co infection was 2.9 % which is in line with our study, whereas in a study by Fairlie et al.[16] from South Africa, HIV prevalence was observed in 52 % of paediatric TB cases. These differences may be attributed to the overall prevalence of HIV infection in respective region. HIV-infected children are likely to have higher risk of tuberculosis exposure because of higher prevalence of the disease in HIV-infected adults. Further, children with HIV are more likely to be investigated for TB. The presence of HIV co-infection compounds the well-recognized challenges of reaching a definitive diagnosis in children with suspected TB.

In our study, 39.6 % cases were microbiologically confirmed TB and the rest were clinically diagnosed. In a study by Swaminathan et al.[17] in 2008, 7.9 % were microbiologically confirmed TB. Schopfer K et al.[18] in 2014 and McIntosh AI et al.[19] in 2018 had documented microbiologically confirmed TB in 22.5 % and 27.8 % respectively. As the years are advancing, the microbiologically confirmed TB detection rate is increasing. But still majority of the cases of paediatric tuberculosis are diagnosed clinically rather than microbiologically. Clinical diagnosis being nonspecific and considerable inter reader variation in radiological findings[20] prompts for a diagnostic technology of a high-positive predictive value. Microbiological confirmations would help in giving a clearer

picture for diagnosis and prognosis of disease in the course of treatment.[21] Further they are helpful to determine the drug resistance pattern initially before the start of the treatment.

13.7 % of the paediatric TB cases were drug resistant in our study. Raizada N et al.[13] did a study on 3340 paediatric TB cases of which 8.8 % of the cases found to be drug resistant. In contrast to this study, Sanjay K Jain et al.[22] reported higher percentage (34.6 %) of drug resistant TB. In our study, 11.7 % are rifampicin resistance. In a similar way, rifampicin resistance of 11.4 % was observed by McIntosh AI et al.[19] In a study by Das PK et al.[23] the point prevalence of RIF resistance TB among the detected found to vary between 13 % and 15 % with a seasonal predominance during summer months.

In our study, 1.4 % are multi drug resistance and 0.6 % are INH resistance alone. In a study by Swaminathan S et al.[17] the prevalence of MDR TB was 4 % and isoniazid resistance was 12.6 % and Yuen M et al.[24] also observed higher percentage (8 %) of INH resistance. Still more number of suspected TB cases should be subjected to newer molecular methods to identify more cases of drug resistant paediatric TB. In our study, majority (92.3 %) had a favourable outcome and 7.7 % had a poor outcome of which 12 (1.8 %) cases died during the treatment. In line with our study Tao N et al.[12] documented a favourable outcome of 94.2 % and a poor outcome of 5.8 % with 0.2 % deaths. Similarly, 91.7 % favourable outcome was reported by Alavi et al.[25] in Iran and 80.1 % was reported by Hailu et al.[26] from Ethiopia. In contrast to our study, Sanjay K Jain et al.[23] reported higher percentage of death rate of 12 % (3 out of 26). Higher death rate reported in their study may be due to small sample size. Strength of our study is including adolescent age group in the study subjects, as studies are less in this specific age group.[27]

CONCLUSIONS

Diagnosis of TB is very challenging in young children and current tools are inadequate. Drug resistant TB is on the rise which is of more concern now. Furthermore, the presence of HIV co-infection compounds the well-recognized challenges of reaching a definitive diagnosis in children with suspected TB. Majority of the paediatric tuberculosis are diagnosed clinically rather than through microbiological confirmation. Majority had a favourable outcome. Efforts should be made to further improve the sensitivity of diagnostic methods, so that it will be possible to effectively diagnose paediatric TB and determine the drug resistance pattern before starting the treatment. TAM-TB assay-T cell activation marker assay is a novel immunodiagnostic test. This TAM-TB assay uses loss of CD27 expression on *Mycobacterium tuberculosis* specific CD4 T cells as a marker of active tuberculosis. As collection of sputum is a great challenge, non-sputum based diagnostic techniques are considered as promising in the diagnosis of paediatric tuberculosis.

Limitations

Limitations of our study are failure to describe the prevalence of different types of extra pulmonary forms of tuberculosis because of limited recorded data. Additional studies are needed to determine more accurate treatment outcome of paediatric TB in this population.

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