Spectrum of Paediatric Tuberculosis at a Tertiary Care Children`s Hospital in Kashmir: A Prospective Study

Ayaz Ahmed Kakroo[1], Shafat Ahmad[2], Mushtaq Ahmad Wani[3]

ABSTRACT

Introduction: Paediatric tuberculosis (TB) accounts for10-15% of all TB with pulmonary TB and extra-pulmonary TB contributing to 70-80% and 20-30% respectively in children. Incidence of EPTB is on rise as reported in recent studies. No such study on paediatric TB has been conducted in Kashmir valley before. Current research aimed to study the spectrum of paediatric TB in Kashmir valley and categorize children treated for TB into Definite TB, Probable TB, Possible TB and No TB.

Material and Methods: Children with suspected TB aged >1month upto 18 years were prospectively enrolled at a tertiary care hospital in Srinagar, Jammu and Kashmir, India over a period of 2 years.

Results: overall 136 children received anti-tuberculosis treatment (ATT) which included 78 (57.35%) cases of pulmonary TB and 58 (42.65%) cases of EPTB. Tubercular meningitis (TBM) 21 (36.2%) was the most common form of EPTB followed by abdominal tuberculosis 14 (24.13%), tuberculous lymphadenopathy 11(18.96%), tuberculous pleural effusion 9(15.52%) and miliary TB 3(5.2%). A total of 60(44%) children had bacteriological evidence of TB (definite TB), 67 (49.3%) were diagnosed on clinical grounds (Probable TB) and TB couldn't be ruled out in 9 (6.7%) cases. Only 36 (26.47%) children were <5 year old, 65(47.8%) children were male, 112(82.35%) children were malnourished. BCG scar was present in 95(69.83%) cases and 56 (41.2%) were tuberculin skin test (TST) positive. History of TB contact was present in 65(47.8%) cases and none of the child was HIV positive.

Conclusion: Although Extra-pulmonary TB is increasing, Pulmonary TB is still the most common type of paediatric TB. BCG offers some protection against severe forms of TB and Young children are at increased risk of severe forms of TB.

Keywords: Tuberculosis, Paediatric, Disease spectrum, Kashmir

INTRODUCTION

India accounts for one-fourth of the global TB burden. Globally, about 1 million cases of paediatric TB are estimated to occur every year with more than one lakh estimated deaths every year.[1] It is one of the top ten causes of childhood mortality.[1] In 2014, WHO reported that 70-80% of children with TB have pulmonary tuberculosis.[2] Some national studies have reported increasing incidence of EPTB in children.[3,4,5] Till date no study has been done in this regard in Kashmir valley. Therefore, we conducted a hospital based prospective observational study to document the current trend in spectrum of paediatric TB and to classify TB cases into Definite TB, Probable TB, Possible TB and No TB.

MATERIAL AND METHODS

The study was conducted from October 2016 to September 2018 in the department of paediatrics at GB pant hospital, Government Medical College Srinagar, Jammu and Kashmir after taking institutional ethics committee approval.

Inclusion criteria: The study was conducted on children aged >1 month upto 18 years admitted with suspicion of tuberculosis. Suspected TB was defined as per Indian Academy of Paediatrics (IAP)- RNTCP Consensus guidelines 2015[6]: Persistent fever and/or cough >2 weeks, unexplained weight loss/no weight gain in the past 3 months (loss of weight is defined as loss of >5% body weight as compared to highest weight in the last 3 months), history of contact with infectious TB case (in a symptomatic child contact with a person with any form of active TB within the last 2 years), presence of organ specific symptoms and signs-painless swelling of lymph node(s), pain and swelling in the joint, spine gibbus, neck stiffness, disorientation. Tubercular meningitis was staged as per British Medical Research Council staging.

Exclusion criteria: Children empirically on anti-tuberculosis treatment (ATT) without supporting evidence of TB and those in whom informed consent could not be obtained were excluded from the study.

Definitions

Definite TB: Children in whom bacteriological confirmation of mycobacterium tuberculosis (MTB) by microscopy, culture or CBNAAT was achieved.

Probable TB[7,8,9]: Children not showing improvement with antibiotic treatment (antibiotics other than those active against MTB) for at least 2 weeks follow up and any one of the following:

1. Clinical picture of meningitis and any one below:
   - CSF (any two present: 10-500WBC/mm3,

[1]Senior Resident, Department of Pediatrics, SHKM, GMC, Nalhar, [2]Associate Professor, Department of Pediatrics, GMC, Srinagar, [3]Senior Resident, Department of Pediatrics, SHKM, GMC, Nalhar, India

Corresponding author: Mushtaq Ahmad Wani, Room No. 101, F1 Block, SHKM, GMC, Nalhar, Nuh, Haryana, India

How to cite this article: Ayaz Ahmed Kakroo, Shafat Ahmad, Mushtaq Ahmad Wani. Spectrum of paediatric tuberculosis at a tertiary care children`s hospital in Kashmir: a prospective study. International Journal of Contemporary Medical Research 2019;6(12):L4-L8.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.12.22

lymphocytes >50%, protein >100mg/dl, glucose <40 mg/dl)
- Head CT/MRI (any present: meningeal enhancement, ring enhancing lesi on/tuberculoma and hydrocephalous)

2. Abdominal USG or CT scan (any present: matted bowel, ascites, lymphadenopathy, hepatosplenomegaly)
3. Chest X-ray consistent with TB: Hilar/mediastinal Lymphadenopathy (LAP), miliary shadows, fibro-cavitatory lesions.
4. Pleural effusion and pleural fluid analysis showing (any two present: 100-100 WBC/mm3, protein >200mg/dl, glucose <40mg/dl)
5. Clinical findings: cervical lymphadenopathy (LAP) with sinus formation.
6. Histogy: Caseating granuloma, gaint cells or otherwise consistent with TB as per pathologist.

No TB: Complete resolution of symptoms in ≤2 weeks of antibiotic therapy.

Possible TB: All others where TB could not be ruled out.

Study procedure: Detailed history and physical examination were performed on each child. Each child was thoroughly assessed for the presence of BCG scar, contact with TB patient within the last 2 years, infections and diseases predisposing to TB (Measles, steroid therapy and immunosuppressents) and nutritional status (Children <5 year were assessed with IAP classification of malnutrition and children aged 5-18years were assessed by using revised 2015 IAP BMI (Body Mass Index) charts separate for Indian children. Relevant laboratory investigations were done: Screening for HIV infection, standard Tuberculin skin test (TST) (0.1ml of 2TU of PPD RT23, Arkray healthcare Pvt. Ltd and an induration of ≥10mm read between 48-72 hours was considered positive) and a Chest X-ray were done in each case. Chest X-ray was independently reported by a radiologist. Ultrasonography (USG), Computed tomography (CT) and magnetic resonance imaging (MRI) when indicated. Pulmonary samples included gastric aspirates and induced/non-induced sputum and when indicated appropriate extra-pulmonary samples (cerebrospinal fluid, FNAC of lymph nodes, pleural fluid and ascetic fluid) were obtained, by following IAP-RNTCP programme management protocols, for bacteriological confirmation of MTB by Ziehl neelsen staining and Lowenstein Jensen medium culture. Genotypic method, GeneXpert (Cepheid, Sunnyvale, CA; rifampicin DST) was also utilized for detection of MTB nucleic acid.

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel 2007). Continuous variables were expressed as mean± SD and categorical variables were summarised as frequencies and percentages. Software SPSS 22 version was used for statistical analysis. Chi-square test was applied for comparing categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

We enrolled 223 children in this study. On subsequent evaluation, TB was ruled out in 87 (39%) cases and 136(61%) children were treated for tuberculosis; 60/136(44.1%) were found to have Definite TB, 67/136 (49.3%) had probable TB while TB could not be ruled out in 9 (6.6%) cases and they were classified as possible TB.

Seventy eight (57.35%) children had pulmonary TB and 58 (42.65%) had extra-pulmonary TB. In children with pulmonary TB, parenchymal involvement was observed in 39/78 (50%) children of which 6 children had cavitatory lesions, parenchymal and lymph node disease was observed in 24/78(30.8%) cases with associated cavitations in 3 children and 15/78 (19.2%) children had only lymph node involvement.

The most common disease manifestation in children with

BCG status	Pulmonary TB	Extra-Pulmonary TB	P value
Immunized	64	31	0.002
Unimmunized	16	25	0.0021

Table-1: BCG status

Nutritional status	TST +ve	TST –VE	Total	P value
Malnourished	40	72	112	<0.001
Normal	13	11	24	0.57
Total	53	83	136	

Table-2: Tubercilin skin test and nutritional status.

TB type	1mo-5 yr		6-11 yr		12-18 yr		Total		P value
	M	F	M	F	M	F	M	F	
Pulmonary TB	10	12	14	13	13	16	37	41	0.693
TB meningitis	3	5	4	4	2	3	9	12	0.547
Abdominal TB	0	0	2	6	1	5	3	11	0.018*
TB lymphadenitis	2	1	7	1	0	0	9	2	0.024*
TB pleural effusion	0	0	3	0	4	2	7	2	0.008*
Miliary TB	0	3	0	0	0	0	0	3	0.025*
Total	36		54		46		65	71	

* statistically significant.

Table-3: Baseline characteristics of children treated for TB

TB type	TST +ve	Undernourished	TB exposure		BCG Scar present
			IFC	EFC	
Pulmonary TB	37	65	14	26	64
TB meningitis	3	19	3	5	8
Abdominal TB	6	14	3	2	10
TB Lymphadenitis	6	8	3	4	8
TB pleural effusion	4	3	1	1	5
Miliary TB	0	3	1	2	0
Total	56	112	25	40	95

Table-4: Baseline characteristics of children treated for TB.

extra-pulmonary TB was tubercular meningitis (21/58, 36.2%) of whom 17 cases presented in Stage II and 2 cases each presented in stage I and III of TBM. Abdominal TB was observed in 14(24.14%) children with 10, 2 and 2 cases in ascitic, plastic and intestinal types respectively. Cervical Lymph node involvement was observed in 11 (19%) cases. Tuberculous Pleural effusion was documented in 9 (15.52%) children; one child had massive fluid collection with mediastinel shift. Three children (5.2%) had disseminated/ miliary disease, all the three had miliary TB picture on chest X-ray with one having pericardial effusion and other two with tubercular meningitis (TBM). No cases of osteo-articular TB, urogenital TB and cutaneous TB were observed in the study.

Bacteriological confirmation of tuberculosis was obtained in 40/78 (51.3%) cases of pulmonary TB. In children with extra-pulmonary TB, bacteriological confirmation was achieved in 20/58 (34.48%) with yields of 7/11 (63.64%) in tuberculous lymphadenopathy, 4/14 (28.57%) in abdominal TB, 4/21 (19%) in TBM, 2/9 (22.2%) in pleural effusion and 3/3 (100%) in miliary TB cases.

The median age of children treated for tuberculosis was 8.1±4.4 years. Children were divided into three age groups to study the impact of age on spectrum of TB. Maximum number of TB cases were observed in 6-11year age group (54, 39.7%) followed by 12-18year age group (46, 33.8%) and 36 (26.47%) children with TB aged ≤ 5years. Pulmonary TB was more common in children aged ≥6 years (56/78, 71.8%). Of 9 children with cavitatory lung lesions, one case was reported in an infant (with underlying immunodeficiency) and the remaining 8 cases were observed in children aged >10years. Intra-thoracic lymph node involvement was more common in children aged ≤5 years (10/15, 66.7%). All cases of Pleural effusions and abdominal TB were observed in children aged ≥6 years. TBM was most frequently documented in children aged 3-9 years (16/21, 76.2%). All cases of miliary TB were observed in children between 3-5 years of age. Tuberculous lymphadenitis was more frequent in children aged 4-11 years (8/11, 72.7%).

Of 136 children with TB, 65 (47.79%) were male and 71 (52. 2%) were female. In abdominal TB (11/14, 78.5%) and miliary TB (3/3, 100%) more females were affected than males while as in tubercular pleural effusion (7/9, 77.78%) and tubercular lymphadenitis (9/11, 81.8%), males were more affected than females. However, no gender predilection was observed for pulmonary TB and TBM.

BCG scar was present in 95 (69.85%) cases indicating a low BCG coverage. Of these BCG vaccinated children, 64/95(67.4%) had pulmonary TB and 31/95 (32.6%) had extra-pulmonaryTB. In BCG non-vaccinated group, 16/41(39%) had pulmonary TB while as 25/41(61%) had extra-pulmonary TB. Severe forms of TB (miliary TB and TBM) were more common in the BCG non-vaccinated group (3/3miliary, 13/21TBM) as shown in Table -1.

Hundred twelve (82.35%) children were malnourished which included 31/36 (86.11%) children aged <5years (Grade 1&2=21; Grade 3&4=10) and 81/100 (81%) children aged ≥5years.

Tuberculin skin test (TST) was positive in 56/136 (41.2%) children treated for TB. The positivity of TST in pulmonary TB cases was 47.4% (37/78) and 32.7% (19/58) in extra-pulmonary TB cases. Among extra-pulmonary forms of TB, TST positivity was highest in tuberculous lymphadenitis 6/11 (54.5%) followed by tuberculous pleural effusion (4/9, 44.44%) and lowest in miliary TB (0/3, 0%). TST positivity was also low in TBM patients (3/21, 14.28%). Among malnourished children, TST was positive in 40/112 (35.7%) cases and negative in72/112 (64.28%) cases while as in children with adequate nutritional status, TST was positive in 13/24 (54.16%) children and negative in 11/24 (45.83%) children. The table below shows the TST results in undernourished and normal children (table-2).

We could trace the source of infection (contact history) in 65/136 (47.8%) cases treated for TB of which 25 had intra-familial and 40 had extra-familial contact sources. The table-3 shows the characteristics of the TB patients in the study.

Fever (88.2%), weight loss/not gaining weight (72.8%), anorexia (65.4%) and cough (56.6%) were the main presenting symptoms. Fever and irritability were the presenting complaints in three TBM cases aged around 3-3.5 years. One child with TBM presented with headache, sixth cranial nerve palsy along with constitutional symptoms. Fundus examination in one TBM case (presented in stage 3) revealed choroid tubercles. Abdominal pain was present in all cases of TB abdomen and ascetic type of abdominal TB was common in girls (10/14). Cyanosis and pericardial effusion were the presenting feature in one miliary TB case. Most children with pleural effusion had some degree of tachypnea (table-4)

DISCUSSION

In 2016 WHO reported that about one million cases of paediatric TB occur every year accounting for 10-15% of all TB.[1] In 2014, WHO reported that 70-80% of children with TB have pulmonary involvement and the remaining have extra-pulmonary TB.[2] In our study we observed that pulmonary TB accounted for approximately 64% of cases and the remaining 36% of cases were contributed by extra-pulmonary TB. Our observation is in comparison with many Indian studies. Kamath et al reported pulmonary TB and EPTB in 60% and 40% cases respectively.[10] Kabra et al also reported higher prevalence of pulmonary TB (59.5%) than EPTB (40.5%).[11] Sushamabai and Devi observed pulmonary TB and EPTB in 72.6% and 18.96% cases respectively.[12] However, some Indian studies report higher prevalence of the EPTB than pulmonary TB.[3,4,5]

The literature studied to know the relative prevalence of various forms of EPTB from Indian studies revealed varying results. Gosai et al and Jain et al reported TBM as the most common form of EPTB in children accounting for 46% and 75% cases respectively.[13,14] Kamath et al documented lymph node TB as the most common form amounting for 42% of all EPTB cases.[10] Vishwanath et al reported TB lymph node (15.2%) and TBM (13.4%) as the most common types of EPTB.[15] TBM (36.2%) and abdominal TB (24.14%) were the most common forms of EPTB in our study.

As per epidemiology of TB, risk of progression of TB infection to disease and the severity of TB is more in children aged upto 5 years.[16] The risk again increases during adolescence.[16] In our analysis we observed that the most common TB affected age group was 6-11 years. A possible reason for involvement of higher age group could be increased mobility of children within the community around the age of 4-5 years and, therefore, increased risk of infection and re-infection. This fact is also supported by the finding that 40/65 (61.5%) TB contacts, in our study, were extra-familial. Various recent Indian studies also report TB disease in higher age groups (10-16 years).[17,18,19] The male: female ratio varied from 0.8:1 to 3.4:1 in different studies.[20,21] In our study, the male: female ratio was 0.9:1.

As reported by Marais et al, intra-thoracic lymph node involvement was most common in children <5 years of age (10/15, 66.7%) in our study also.[16] Vimlesh S mentions that neuro-tuberculosis is common in boys below the age of 5 years with peak incidence between 3-5 years of age.[22] We observed TBM to be more common in children between 3-9 years age (15/21, 71.4%) with no gender predilection (P value 0.54). All cases of abdominal TB were noted above the age of 5 years, girls were predominantly affected (11/14, 78.6% P value 0.18) and ascetic type (10/14, 71.4%) was the most common form observed in our study. Vimlesh S mentions that ascetic type is most common form of abdominal TB in children and is less common below 5 years of age.[22] Our findings on abdominal TB are also supported by a Turkish study which reported ascetic type of abdominal TB in 26/35 (74.3%) cases with mean age of patients around 9.7±4.36 years and female preponderance (19/35, 54.3%).[23] Tuberculous lymphadenitis occurs with equal frequency in all paediatric age groups except in infancy where it rarely occurs.[22] In our analysis, we did not observe TB lymph node in children <2 years and >11 years but the disease showed predilection for boys (9/11, 82% P value 0.24). In our study, no case of tuberculous pleural effusion was observed in children <5year age and maximum incidence was noted between 12-18years of age (6/9, 66.7%) and boys were predominantly affected (7/9, 77.8% P value 0.008). Marais et al also noted a slight male predominance and a higher age of affliction (>5 years) in tuberculous pleural effusion.[16]

In this study, BCG coverage (69.85%) was below the national standard of 86%. Pulmonary TB was more common than extra-pulmonary TB in BCG vaccinated group (64, 67.4% Vs 31, 32.6%; p value 0.002). In BCG non-vaccinated group, EPTB was observed to be more common than pulmonary TB (25, 61% Vs 16, 39%; P value0.002). Moreover, BCG coverage was low (0%-38.1%) in severe forms of TB (TBM and miliary TB) while as in less severe forms of TB, BCG coverage was between 55%-82%. This can be explained by the fact that BCG provides an overall low protection against TB but it has good protection against severe forms of TB.[5]

There is a significant burden of malnutrition in children, especially in developing countries. This was also reflected by high prevalence of malnutrition (82.35%) in our study. Malnutrition causes impairment in functioning of the immune system and thus provides a favourable environment for TB disease.

About 41.2% of children diagnosed with TB were TST positive in our study. TST positivity rate was relatively low in EPTB (19/58, 32.7%) than pulmonary TB (37/78, 47.4%) but this difference was not found to be statistically significant (P value 0.085).Further, TST positivity was low in severe forms of TB (3/24, 12.5%; TBM & miliary TB) than other forms of TB (53/112, 47.3%). The study by Muley et al showed overall TST positivity of 69% with positivity rate more in pulmonary TB (75%) than EPTB (65%). In the same study, the TST positivity rate was maximum in tuberculous lymphadenitis (80%) and least in disseminated TB (0%).[24] These observations are consistent with our findings.

In our observation, large number of malnourished children with TB had negative TST (72/112, 64.2%) and the difference between the number of TST positive and TST negative malnourished children was statistically significant (P value <0.001) . In children with adequate nutritional status, almost equal number of cases had positive (13/24, 54.16%) and negative (11/24, 45.83%) TST results. Low TST sensitivity in malnourished children may be because the T-cell mediated immunity is greatly impaired in malnourished children such that the efficacy of TST is greatly reduced. A study by Kumbhojkar SM et al reported that the mean induration of mantoux test was more in normal children than in malnourished children.[25] Therefore, while a positive mantoux test is helpful, a negative mantoux test does not rule out TB especially in malnourished children.

CONCLUSION

This study provides a comprehensive picture of disease spectrum in children treated for TB in a tertiary care paediatric hospital in a TB endemic area. While Pulmonary TB is still the most common type, EPTB is showing an increase. TBM predominates among EPTB cases in hospitalized children. Young children are at high risk of developing severe forms of TB, emphasising the importance of preventive chemotherapy in this high risk group. BCG offers some protection against severe forms of tuberculosis.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 15-11-2019; **Accepted:** 12-12-2019; **Published:** 29-12-2019