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Original Article

Childhood Tuberculosis and its Relation with Nutrition: A five Year Retrospective Study

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ABSTRACT:

Introduction: Tuberculosis is the sixth leading cause of mortality in Nepal. Childhood tuberculosis consisted 5.54% of newly registered 32,056 cases in 2016-17. Malnutrition is a predictor of tuberculosis and is associated with poorer outcomes. This study evaluates the clinico-epidemiologic profile of childhood tuberculosis and its relation to nutritional status. **Methods**: This was a retrospective review of 60 cases of tuberculosis admitted over a period of five years. Details regarding demographics, anthropometry, symptomatology and examination findings were retrieved. Diagnosis was categorized as pulmonary, extra-pulmonary and disseminated tuberculosis. Findings of various investigations were noted. Nutritional status of the patients was assessed using the WHO standard charts. Association of malnutrition and anemia with types and severity of tuberculosis was assessed. **Results**: A total of 60 patients were included in the study. Mean age was 7.9 years (SD = 4.6). The commonest presenting symptom was fever (83.3%) followed by decreased appetite (33.3%) and weight loss (26.7%). Cough was the predominant symptom in pulmonary tuberculosis (45%). Only eight cases were bacteriologically confirmed. Underweight, wasting and stunting were observed in 68.4%, 63.3% and 53.3% of cases respectively. Wasting was significantly associated with severe forms of tuberculosis ($p = 0.03$). Anemia was present in 89.5% of under five children ($p = 0.02$). **Conclusion**: Malnutrition often co-exists in a significant proportion of children with tuberculosis. Diagnosis in resource limited settings heavily relies on clinical suspicion and supporting investigations. Anemia is significantly associated with childhood TB, especially under five children.

Keywords: anemia, malnutrition, Nepal, pulmonary, tuberculosis

INTRODUCTION:

Tuberculosis (TB) is one of the top 10 causes of mortality worldwide and is the sixth leading cause in Nepal.[1,2,3] In 2016, 6.3 million new cases of TB were reported globally.[4] This amounted to 61% of the estimated incidence of 10.4 million out of which one million (10%) was estimated to be in children. [3,4] In Nepal, childhood TB consisted 5.54% of newly registered 32,056 TB cases in 2016/2017.[4]

Diagnosis and treatment of TB in children is challenging because the bacteriologic confirmation in childhood TB is low.[5,6,7,8,9] Its management is largely directed by the epidemiological and clinical characteristics. The epidemiology of TB in children is poorly understood and the clinical manifestations are heterogeneous.[10] As such, a better understanding of the clinico-epidemiolgic profile of childhood TB especially in resource limited countries will contribute significantly in preventive and curative aspects.

In people infected with M. tuberculosis, the probability of developing clinical disease rises much higher with the co-presence of risk factors as malnutrition, diabetes and HIV infection.[1,3] The

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prevalence of malnutrition is also observed to be high in children dwelling in TB endemic countries.[11] In Nepal, 11% of wasting, 30% of underweight and 37% of stunting are seen in children below five years of age. Malnutrition is a predictor of TB disease and is associated with poorer outcomes. Despite significant burden of both malnutrition and childhood TB in Nepal, there is still a paucity of published studies on clinico-epidemiologic features of childhood TB and their relationship with malnutrition. This study aims to fulfill this gap by evaluating the clinico-epidemiologic spectrum of childhood TB and exploring its relationship with nutritional status.

METHODS:

This retrospective study was conducted from August 2017 and February 2018 after approval from the Institutional Review Committee. A review of cases was done for children less than 14 years of age admitted in the Department of Pediatrics and Adolescent Medicine, Lumbini Medical College and Teaching Hospital (LMCTH) with the diagnosis of TB from April 2013 to February 2018. Also, the numbers were confirmed after performing a cross check with the Directly Observed Treatment Short-course (DOTS) clinic register in the hospital. Eighty two such cases were identified and their medical records were checked for completeness of details required for the study. The records were then screened for eligibility for diagnosis of TB as per the WHO diagnostic approach and the National Childhood TB Management Guidelines, 2074.[1,12,13] A total of 60 cases met the criteria and were included in the study for the subsequent analysis.

Details regarding demographics, anthropometry, symptomatology, examination findings, laboratory, radiological, microbiologic and histopathologic investigations were extracted using a pre-designed proforma. Clinical history and physical examination findings were described. In all cases, mantoux readings were done and a positive reading was defined as five or more mm if HIV-infected, severe acute malnutrition, and immunosuppression, otherwise 10 or more mm.[1] Isolation of bacilli was done with AFB smears of sputum or gastric lavage specimens, Fine Needle Aspiration Cytology (FNAC) specimen, and Gene Xpert MTB/Rif when available, as culture facilities are not available in the hospital. Radiological investigations performed were chest X-ray for all cases, CT head in CNS TB, ultrasonography of abdomen and chest in abdominal and pleural TB respectively. Body fluid examination with Adenosine deaminase (ADA) levels was noted in cases of pleural, pericardial, abdominal and CNS TB. ADA was considered significant when >60 IU/L in pleural fluid, >40 IU/L in pericardial fluid, >40 IU/L in ascitic fluid and >10 IU/L in CSF.[1]

History of household as well as non-familial contact with TB cases was ascertained. Presence or absence of a BCG scar and HIV status was noted. Diagnosis was confirmed after bacterial isolation. In the absence of bacteriologic confirmation, diagnosis was based on radiographic, laboratory and clinical data. Clinical data included exposure to household members with pulmonary TB, presenting symptoms, inadequate response to routine empiric antibiotics, a positive mantoux test and response to ATT. TB was categorized as pulmonary, extra-pulmonary and disseminated tuberculosis based on the clinical characteristics. Severe TB was defined as meningeal and disseminated TB, which also included cases of miliary TB.[14]

Nutritional status of the patients was assessed using the WHO Multicentre Growth Reference Study (MGRS) based Z scores charts.[15,16] Height for age was assessed for all subjects and Z-score was categorized as: normal if between -2 to +2; stunted if between -2 to -3; severely stunted if less than -3. Weight for age Z-score was used for children less than 10 years old only and categorized as: normal if between -2 to +2; underweight if between-2 and -3; severely underweight if less than -3.Weight for age reference is not available for children >10 years of age. BMI for age was assessed in all cases and was categorized as: normal if between -2 to +2; moderate wasting if between -2 to -3; severe wasting if less than -3.

Presence of anemia was also noted. Anemia was defined according to the WHO guidelines which is hemoglobin level (gm/L) >2SD below the mean for the child's age and sex. The cutoffs are < 110 gm/L for 6 months to 5 years; <115 gm/L for 5-11 years and <120 gm/L for 12-14 years.[17]

Data analysis was done using Statistical Package for Social Sciences (SPSS™) software version 20. Demographic details, clinical characteristics and investigations were elaborated using descriptive statistics. Association of malnutrition and anemia with age distribution, types of TB and severe form of disease was assessed using Chi-square test and Fisher exact test where appropriate. P value of < 0.05 was considered significant.

RESULTS:

Demographics:

Sixty children aged six months to 14 years were included in the study. Mean age at presentation

was 7.9 years (SD = 4.6). Of these, 60% were males and 40% were females. Majority of the children belonged to Dalit caste (46.6%) followed by Brahmin-Chhetri (25%) (Table 1). All of these cases were from the Western region of the country, with 88.5% from Lumbini zone, 6.6% from Gandaki zone and only one case from Rapti and Dhaulagiri each. Household contact as well as non-familial contact with TB cases were positive in 23% of the cases which were mainly grandparents, parents and multiple contacts including neighbors.

Clinical characteristics:

The commonest presenting symptom was fever, seen in 83.3% of the cases. Of these, 50% had a fever of more than two weeks duration and 33.3% had fever of less two weeks duration. Other non-specific symptoms common to most types of TB were decreased appetite in 33.3% of the cases and weight loss in 26.7% of the cases. Besides the non-specific features, cough was the predominant symptom in pulmonary TB seen in 45% of the cases. Children with CNS involvement presented with headache in 15% of cases and vomiting in 13.3% of the cases. Loss of consciousness and seizures was seen in 11.7%. Abdominal distention was seen in 6.7%, hepatomegaly in 6.7%, and hepatosplenomegaly in 11.7% of the cases. These symptoms were seen in children with abdominal TB and disseminated TB. Significant lymphadenopathy was seen in 18.3% of the cases. Eighteen cases (30%) had severe TB.

Table 1: Socio-demographic and clinical characteristics (N = 60)

Characteristics	Categories	n (%)
Age (years)	0 - 4	19 (31.7)
	5 - 14	41 (68.3)
Gender	Male	36 (60)
	Female	24 (40)
Ethnicity	Dalit	28 (46.6)
	Janajati	14 (23.3)
	Brahmin and Chhetri	15 (25)
	Madhesi	2 (3.3)
	Others	1 (1.6)
Nutritional status	Underweight	26/38 (68.4)
	Wasted	38 (63.3)
	Stunted	32 (53.3)
TB contact	Positive	14 (23.3)
	Negative	46 (76.7)
BCG scar	Positive	39 (65)
	Negative	21 (35)
Pulmonary TB	Bacteriologically confirmed	4 (6.7)
	Clinically diagnosed	17 (28.3)
Extrapulmonary TB	Pleural	15 (25)
	Pericardial	1 (1.7)
	Abdominal	1 (1.7)
	CNS	11 (18.3)
	Lymph nodes	4 (6.7)
Disseminated TB		7 (11.7)

Investigations:

Bacteriological confirmation could be done in 13.3% (n = 8) cases. Of these three were smear positive, four were positive on Xpert MTB/RIF, and one was AFB positive on FNAC. Xpert MTB/RIF was done on gastric lavage and sputum samples only. Mantoux test was positive in 21.7% children. ADA levels were performed on 29 body fluids, i.e. in 48.3% of cases. Of these, 14 were pleural fluid, nine were CSF and three were pericardial and ascitic fluids each. Significant elevations were noted in 28.6% pleural fluids, 55.6% of CSF, 66.7% of pericardial fluid and 33.3% of ascitic fluid. FNAC of lymph nodes were performed in seven cases, out of which four were lymph node TB and three were part of disseminated TB. HIV screening was only performed on 63.3% of cases, out of which none were positive (Table 2). The chest X-ray and CT findings are shown in Table 3.

Nutritional status:

Weight for age was applicable for children <10 years of age, i.e in 38 cases. Of these, 26 cases (68.4%) were underweight. Wasting was noted in 63.3% of cases and stunting was seen in 53.3% of cases (Table 1). Wasting was significantly associated with severe forms of TB, p = 0.03 (X^2 = 4.4, df = 1) (Table 4). Relationship between wasting and types of TB, age distribution did not reach statistical significance. Similarly, stunting did not show a statistically significant association with age distribution, types of TB and severe forms of TB. Anemia was observed in 89.5% of children below 5 years and this association was statistically significant, p value = 0.02 (X^2 = 5.02, df = 1) (Table 4).

DISCUSSION:

The mean age of presentation of childhood TB was 7.9 years (SD = 4.6). Of these, 68.3% were between five to14 years of age and 60% were males. Majority of the children belonged to the Dalit caste. A similar distribution was reported by Shrestha et al. where at presentation, mean age was 7.4 years (SD

Table 2: Investigations and diagnostic procedures (N = 60)

Investigation	Results	n(%)
AFB (Sputum/ Gastric lavage)	Positive	3(4.9)
	Negative	57(93.4)
Xpert MTB/RIF (sputum/Gastric lavage) (n=10)	Positive	4(6.7)
	Negative	6(10)
	Not available	50(83.3)
Mantoux	Positive	13(21.7)
	Negative	47(78.3)
FNAC lymph nodes (n=7)	AFB positive	1(14.2)
	Caseating necrosis	1(14.2)
	Granulomatous inflammation	2(28.6)
	Reactive lymphadenitis	3(42.8)
Body Fluid ADA Positive (n=29)	Pleural	28.6%
	Pericardial	66.7%
	Ascitic	33.3%
	CSF	55.6%

Table 3: Radiological findings (N = 60)

Modality	Findings	n(%)
Chest X ray findings	Normal	12(20)
	Consolidation	9(15)
	Infiltrates	15(26)
	Pleural effusion	18(30)
	Hilar adenopathy	6(10)
	Cavitation	1(1.6)
	Miliary mottling	2(3.2)
	Cardiomegaly	3(5)
CT findings (n=11)	Normal	7(11.6)
	Hydrocephalus	2(3.3)
	Tuberculoma	2(3.3)

= 3.5) years with 70% of cases between five to 15 years. Sixty-eight percent were males in this study. [10].

History of contact with adult TB cases were elucidated in 23.3% of cases which were mainly family members. Reported TB contacts were seen in 27% of cases in Vietnam and 32.3% of cases in Dhulikhel.[10,14] BCG scar was identified in 65% of the cases. Pulmonary TB comprised 35%, Extra pulmonary TB (EPTB) in 53.4% and disseminated TB was seen in 11.7% of cases. Figures from another center of Western region, Pokhara showed pulmonary TB in 46.3%, EPTB in 41.4%, and disseminated TB in 7.4% of childhood cases.[18] In children between six months to five years pulmonary TB was more common ie., 52.4% and EPTB was more common in five to 14 years of age (79.5%) . Similar findings have been revealed in other centers of the country. [10,18] Most common extra pulmonary site was pleura in 25% of cases. Lymph node TB was seen in 6.7% of cases in our study though it has been reported as one of the commonest extrapulmonary sites of tuberculosis.[18,19] A plausible explanation would be that most uncomplicated lymph node TB are treated on OPD basis and our study included review of inpatient records only which could have led to this under representation.

Diagnosis of pediatric tuberculosis presents a major challenge. Bacteriological confirmation rates are low due to paucibacillary nature of disease but lack of culture facilities and limited investigations in resource constrained settings add to the problem. This was reflected in our study as the diagnosis heavily relied upon three supportive investigations namely microscopy for AFB, mantoux readings and chest X-ray findings. Fluid ADA, CT head and

Table 4: Nutritional status and anemia with age distribution and types of TB

	Stunting		Wasting		Anemia	
Variables	**Absent**	**Present**	**Absent**	**Present**	**Absent**	**Present**
<5 yrs (n=19)	47.4%	52.6%	26.3%	73.7%	10.5%	89.5%
≥5 yrs (n=41)	46.3%	53.7%	41.5%	58.5%	61.0%	39.0%
	p = 0.94, X^2 = 0.006, df = 1		p = 0.26, X^2 = 1.28, df = 1		p = 0.03, X^2 = 5.02, df = 1	
PTB (n=21)	47.6%	52.4%	38.1%	61.9%	9.5%	90.5%
EPTB (n=39)	46.2%	53.8%	35.9%%	64.1%	41.0%	59.0%
	p = 0.91, X^2 = 0.01, df = 1		p = 0.87, X^2 = 0.28, df = 1		p = 0.051, X^2 = 3.8, df = 1	
TB (n=42)	75.0%	65.6%	45.2%	54.8%	33.3%	66.7%
Severe TB (n=18)	25.0%	34.4%	16.7%	83.3%	22.2%	77.8%
	p = 0.43, X^2 = 0.62, df = 1		p = 0.04, X^2 = 4.4, df = 1		p = 0.39, X^2 = 0.74, df = 1	

PTB - pulmonary TB; EPTB - extra pulmonary TB

FNAC were performed in suitable cases. Xpert MTB/RIF was available on the records of cases since mid 2016 and cases prior to this period relied on routine microscopy smears only. Bacterial isolation could be achieved in 13.3% (n = 8) of cases. Similar figures of 8.3% was seen in Dhulikhel 7.3% was observed in Kathmandu in two separate studies.[10,20] However, these studies were conducted in a different time frame thereby, restricting the comparability of the studies. Three out of sixty (5%) tested sputum/gastric lavage samples were positive for AFB on routine microscopy. However, Xpert MTB/RIF was positive in four out of the 10 tested sputum/gastric lavage samples (40%). Interestingly, none of the samples that tested positive on Xpert MTB/RIF showed positive results on routine microscopy. This reflects the superiority of Xpert MTB/RIF over conventional microscopy as described by Detjen KA et al.[21]

Mantoux was found to be positive in 21.7% of cases which was lesser than the rates reported in other studies. Shrestha et al. reported Mantoux positive in 39% of cases in Kathmandu, Shrestha et al. reported positive rates of 48.3%, and Blount RJ et al. reported rates of 51%.[10,14,20] Higher rates of malnutrition in our study and a higher proportion of severe TB cases in our study population could be responsible for the lower rates observed. Estimation of body fluids for significant ADA levels as defined by National Childhood TB guidelines were done in suitable cases and was also taken as a supporting evidence in the diagnosis of TB. Chest X-ray was done in all cases and showed parenchymal lesions in 41% of the X rays with consolidation in 15 % and non-specific infiltrates in 26%. Hilar adenopathy was noted in 10% but milliary shadows and cavitation were seen in 1.6% of the cases only. FNAC was done in 11.6% of cases which included lymph node TB and disseminated TB cases with lymph gland enlargement. CT brain was employed in CNS TB cases along with the CSF studies for supporting evidence of TB disease.

This study revealed that wasting was present in 63% and stunting in 53.3% of the study population. This was much higher than the national figures for malnutrition in children less than five years in the general population shown by the Nepal Demographic Health Survey Report 2016, as the study subjects were a diseased population.[2] Malnutrition is known to exert detrimental effects on host immune responses against mycobacterial infection by impairing various steps of cell mediated immunity and affecting T lymphocyte function and cytokine production.[22,23] Therefore, risk of progression of a localized lesion to progressive disease in increased. Conversely, interactions between organism and host response results in metabolic changes leading to reduction of appetite, nutrient malabsorption and wasting.[24] Such high rates of malnutrition was also reportedly seen in up to 48.8% of pediatric TB cases, in a study done by Shrestha et al. in Nepal Medical College.[20] Severe malnutrition was present in 58.4% of cases of childhood TB in another study done by Verma J et al. in Gwalior, India.[25]

Wasting was observed in a significant proportion of severe TB cases and this association reached a statistical significance, $p = 0.03$ ($X^2 = 4.4$, df = 1). A study done in Vietnam reported malnutrition in 38% of cases (with moderate malnutrition in 17% and severe malnutrition in 21%) which were lesser than our figures.[14] A possible reason would be that the proportion of severe TB cases in this study(17%) was much lesser than the 30% reported in our study. This finding is also coherent with another study conducted by Shrestha S et al. in Dhulikhel Hospital in which they reported more malnutrition in disseminated TB cases than with other diagnosis, $p < 0.001$.[10] Relation between wasting and types of TB did not reach a statistical significance. Also, significant association was not seen between stunting and types of TB and severe disease.

Anemia was seen in 70% of cases in our study across all age groups. It was observed in a significant proportion (89.5%) of under five children with tuberculosis, $p = 0.02$ ($X^2 = 5.02$, df = 10). Anemia is reported in 53% of under five children with a higher proportion between ages six to 23 months (68%) in NDHS Report 2016.[2] Anemia has been reported in several adult studies and iron deficiency and anemia have been postulated to predict mortality in tuberculosis patients.[26] But, there is a dearth of similar evidence in children with tuberculosis. Our study being retrospective in nature could not evaluate the possible causes of anemia, though it has highlighted the high prevalence in children diagnosed with TB at our center. Further studies are required to assess the causative factors and its association with outcome. Anemia was seen in 85.7% of children with PTB and 61.5% of children with EPTB, ($p = 0.051$, $X^2 = 3.8$, df=1). This trend may have been due to the fact that most of the cases of PTB were in children less than five years of age, the age group which had a high prevalence of anemia. Alternatively, to determine a true association between anemia and PTB a suitable prospective

study design with an adequate sample size would be required.

CONCLUSION:

Childhood TB was more prevalent in the socio-economically backward Dalit caste and in children older than five years. Extrapulmonary TB predominated in clinical scenario, with pleural TB comprising one quarter of all the TB cases. Poor nutritional status was identified in more than half of the cases. Anemia was a significant co-contributor to the tuberculosis outcomes, especially in under five population. This study therefore highlights the frequent association of malnutrition and anemia with childhood TB.

ADDITIONAL INFO:

Conflict of interest:

The authors declare that no competing interest exists.

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