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The Spectrum of Childhood Tuberculosis in an African Setting: A Hospital-Based Experience in Bamenda, Cameroon

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What is already known on this topic?

- *Children are particularly vulnerable to severe tuberculosis disease and death following infection.*
- *The diagnosis of tuberculosis is difficult in children.*

What this study adds on this topic?

- *Gene Xpert and smear microscopy confirmed the diagnosis of tuberculosis in 96.2% and 88.5% of the children, respectively.*
- *We noted a high cure rate of childhood tuberculosis and low mortality.*
- *Children aged less than 5 years were found to have 9 times increased risk of mortality.*

ABSTRACT

Objective: Difficulty in confirming childhood tuberculosis leads to late diagnosis and subsequently poor outcomes. This study aimsto determinethe epidemiology, clinical features, diagnostic modalities, and outcomes of childhood tuberculosis at the Bamenda Regional Hospital.

Materials and Methods: This was a retrospective study involving childrenaged between0–15 years with confirmed tuberculosis fromJanuary 1, 2012, to December 31, 2021. We excluded children without proven tuberculosis diagnosis. Data were obtained from files using predesigned data collection forms.

Results: In total, 108 proven cases of childhood tuberculosis were managed in our study period out of which 86 fulfilled our inclusion criteria and were recruited. This gave a prevalence of 4.5% at the Bamenda Regional Hospital. The mean age of the children was 9.6±4.5years. We had a sex ratio of 0.8. The most frequent presenting symptoms were cough (98.8%) and fever (87.2%). Gene Xpert confirmed the diagnosis in 96.2% of the children, smear microscopy in 88.5%, and histopathological analysis in 100% of biopsied specimens. Non-cavitating lesions (43.6%) were the most frequent chest x-ray finding. The majority of the childhood tuberculosis cases were pulmonary (96.5%). Most children (76.7%) were cured and the mortality was 11.3%. The risk of death of children younger than 5 years (P= .015)wasincreased 9 times.

Conclusions: We found the prevalence of childhood tuberculosis to be 4.5% at the Bamenda Regional Hospital. Most children presented with cough, fever, and weight loss. There was a high cure rate and low mortality, and age less than 5 years significantly increased the risk of mortality.

Keywords: Cameroon, Childhood tuberculosis, clinical features, diagnosis, epidemiology, outcomes

INTRODUCTION

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* that most often affects the lungs and is curable and preventable.[1]The World Health Organization estimates that annually about 1.1 million children less than 15 years have TB disease and many more harbor a latent form of infection.[2,3]Children are particularly vulnerable to severe TB disease and death following infection.[4]The true global burden of childhood TB is unknown because it is often difficult to confirm the diagnosis microbiologically.[2,5]The source of transmission to a child is usually an adult with TB positive who should be actively sought.[6]Targets for the United Nations-Sustainable Development Goals call for a 90% reduction in TB deaths by 2030.[7]

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Since childhood, TB reflects recent transmission; its burden can provide a measure of the level of TB control achieved in the community.[3,4]Accurate statistics on pediatric TB cases are difficult to obtain for a multitude of reasons including under-recognition, challenges in confirming the diagnosis, and under-reporting to national TB programs.[3]The difficulty in confirming childhood TB leads to late diagnosis and subsequently poor outcomes. The absence of a standard clinical and radiologic definition of TB in children also causes diagnostic and therapeutic delays.[8]

This study aimsto assessthe epidemiological features (prevalence, sociodemographic features), clinical features (presenting symptoms, duration of symptoms, and physical examination findings), diagnostic modalities (paraclinical characteristics including, Gene Xpert, smear microscopy, histopathological analysis of biopsy, and chest x-ray), outcomes (cure, death, relapse, loss to follow-up), and factors influencing mortality of childhood TB at the Bamenda Regional Hospital (BRH).

MATERIALS AND METHODS

Study Design and Study Site

This was a hospital-based retrospective study conducted at the TB unit of the BRH, a level III hospital in the northwest region of Cameroon fromJanuary 2022 to June 2022.

Study Procedure

We collected data from files of patients managed for bacteriologically proven TB at the TB unit from January 1, 2012, to December 31, 2021, using predesigned data collection forms. The variables obtained were as follows: demographic characteristics (age, sex), history of TB contact, symptoms, duration of symptoms, physical examination findings, paraclinical investigations (Gene Xpert, sputum smear microscopy, histopathological analysis of biopsy, chest x-ray), and informationabout theoutcomes (cure, death, relapse, loss to follow-up, referral).

At the end of daily data collection, completed forms were assessed, validated, coded, and stored. Data were entered into Microsoft Excel 2016 and the information was stored in cloud, on a computer, and on an external drive with a password fixed to maintain confidentiality and safety.

Children aged 0-15 years managed for bacteriologically proven TB at the TB unit from January 1, 2012, to December 31, 2021, were consecutively included in this study (n= 86). Children managed for TB without a confirmed diagnosis or with incomplete files lacking pertinent information for the study were excluded from the study (n= 22).

Diagnostic Procedure of the Patients

The diagnosis of childhood TB in the patients was based on: the child's presenting symptoms, physical examination findings, and paraclinical examination results (including either a positive Gene Xpert, positive smear microscopy, or a positive histopathological analysis of biopsy). Gene Xpert was done using the following specimens: sputum, gastric aspirates, lymph node aspirates, peritoneal fluid, and pleural fluid. Histopathological examination was performed on tissue samples obtained from an axillary mass and from a neck mass.

Ethical Considerations

Ethicalapprovalwas obtained from the Institutional Review Board (IRB) of the Faculty of Health Sciences of the University of Bamenda (No: 2022/0403H/UBa/IRB). An administrative authorization to carry out the research in the North West Region was obtained from the North West Regional Delegation of Public Health. Administrative authorization to carry out the research at the TB Units of the BRH was also obtained from the Director of the hospital.

StatisticalAnalysis

Data were analyzed according to objectives using the Statistical Package for the Social Sciences version 26.0(IBM Corp., Armonk, NY, USA). Descriptive statistics was used to describe data. Continuous variables were expressed as mean and range while categorical data were expressed in frequency (percentages). The coefficient of variation (standard deviation/mean) was used for the normality distribution of numerical continuous data. Mean ± standard deviation was used when numerical data show normality distribution. The data were analyzed using chi-square and a*P*-value of less than .05 was considered statistically significant. The observed variables were tested using univariate and multivariate logistic regression analysis. In multivariate analysis, the independent variables were age group, sex, and human immunodeficiency virus (HIV) status while the dependent variable was outcome.

RESULTS

Prevalence of Childhood Tuberculosis

From January 1, 2012, to December 31, 2021, 2413 cases of TB were treated at the TB unit of the BRH out of which 108 were proven cases of childhood TB giving a prevalence of 4.5%. Out of the 108 proven cases of childhood TB, 86 fulfilled our inclusion criteria and were studied.

Sociodemographic Characteristics of the Children

The mean age of the children was 9.6 (±4.5) years, and the age range was 1 month to 15 years.The highest number of children (58.13%) were of the age group 11-15 years while only 3.49% were <1 year old. Most of the children enrolled were females (55.8%) giving a sex ratio of 0.8 (Table 1).

Clinical Features

The most frequent presenting symptoms were cough (98.8%), fever (87.2%), weight loss (70.9%), and night sweats (62.8%)

Table 1. Sociodemographic Characteristics of the Children with Tuberculosis

Variable	Frequency (n= 86)	Percentage
Age		
<1 year	3	3.5
1-5 years	9	10.5
6-10 years	24	27.9
11-15 years	50	58.1
Total	86	100.0
Sex		
Female	48	55.8
Male	38	44.2
Total	86	100.0

Table 2. Presenting Symptoms of Children with Tuberculosis

Symptoms	Frequency (n= 86)	Percentage
Cough	85	98.8
Fever	75	87.2
Weight loss	61	70.9
Night sweats	54	62.8
Chest pain	36	41.9
Anorexia	33	38.4
Dyspnea	26	30.2
Hemoptysis	5	5.8
Others*	6	7.0

*Others: axillary mass, neck and jaw swelling, epistaxis, back pain, abdominal pain, and abdominal distension.

Table 3. Signs on Physical Examination of Children with Tuberculosis

Signs	Frequency (n= 86)	Percentage
Fever	71	82.6
Chest dullness, crackles, or decreased breath sounds	50	58.1
Enlarged cervical, axillary, and inguinal lymph nodes	33	38.4
Respiratory distress	21	24.4
Ascites	2	2.3
Axillary mass	1	1.2
Neck mass	1	1.2

(Table 2). Most children's symptoms lasted for 1-3 months (41.9%) while 38.4% and 19.8% of the children's symptoms lasted >3 months and <1 month, respectively, before consultation. The most common physical examination signs were fever (82.6%), chest dullness, crackles or decreased breath sounds (58.1%), and enlarged cervical, axillary, or inguinal lymph nodes (38.4%) (Table 3).

Diagnostic Modalities

Gene Xpert was done for 61.6% of the children and was positive for 96.2% of the children. Smear microscopy was done for 70.9% of the children and was positive for 88.5% of the children. Histopathological analysis of biopsy was done for 2.3% of children and was positive for all (100%) of them (Table 4).

Table 4. Laboratory Characteristics of the Children with Tuberculosis

Variables	Frequency (n= 86)	Percentage
Gene Xpert (n = 53)		
Positive	51	96.2
Negative	2	3.8
Total	53	100
Sputum smear microscopy (n = 61)		
Positive	54	88.5
Negative	7	11.5
Total	61	100
Histopathological analysis of biopsy (n = 2)		
Positive	2	100
Negative	0	0
Total	2	100

Non-cavitating lesions were the most frequent finding on chest x-ray (43.6%). The non-cavitating lesions included patchy opacities, miliary opacities, nodules, blunting of costophrenic angle, and hilar adenopathies. The majority of the childhood TB cases were pulmonary (96.5%) TB.

Outcome of the Children

Most of the children (76.7%) were cured while 10.5% died. The number of patients referred to other health facilities and those lost to follow-up were subtracted from total proven childhood TB cases when calculating the mortality rate because their outcome could not be determined. Thus, only 80 children's outcomes could be determined as 1 patient was referred and 5 patients lost to follow-up. Out of the 80 children, 71 were alive and 9 died giving a mortality rate of 11.3%. Of the 9 children who died, all had pulmonary TB, 4 were children living with HIV, and 2 had malnutrition.

Past History of the Children

Very few children (8.1%) had a known contact history with a household member sick of TB while the majority (91.9%) of children's contact history was unknown. Most children (77.9%) were HIV-negative while 22.1% of the children with proven childhood TB were children living with HIV. The majority of the children (83.7%) were vaccinated with the Bacille Calmette-Guerin (BCG) vaccine, no child was unvaccinated with BCG, and 16.3% of children's BCG vaccination status was unknown.

Factors Influencing Mortality

Among all the factors evaluated, age was the only factor which significantly influenced mortality. The risk of death of children aged 0-5 years (adjusted odds ratio = 9.11; $CI_{95(1.53-54.25)}$; P= .015) is increased by 9 times, making it a factor of increasing mortality (Table 5).

DISCUSSION

The prevalence of childhood TB in our study was 4.5%. This prevalence was 2 times lower than the findings of Mirutse et al[9]in Ethiopia which had 8.1%. However, it was almost 3 times higher than the findings of Aketi et al[10]in the Democratic Republic of Congo which had a prevalence of 1.7%. The differences in the prevalence can be attributed to the difference in the study populations as well as the difference in BCG vaccination coverage in the different countries. The BCG vaccination coverage in Cameroon dropped from 80% in 2020 to 77% in 2021.[11]This reduction in the vaccination coverage can be due to intermittent BCG vaccine shortages in the country. The high prevalence in our study can also be attributed to the poor control of adult TB and co-infections with HIV which weakens the immune system.

The majority of the children were females giving a sex ratio of 0.8. This is similar to the findings of Aygün et al[8]in Turkey and Panigatti et al[12]in India. This, however, differs from the findings of Aketi et al[10]in the Democratic Republic of Congo, Gava et al[13]in Brazil, and Kaba et al[14]in Turkey who found cases to be slightly more common in males. The mean age of the children was 9.6 ± 4.5 years. This is close to the finding of Aketi et al[10]in the Democratic Republic of Congo who had a mean age of 8.7 (±4.4) years. This, however, markedly differs from

Table 5. Factors Influencing Mortality

	Outcome		Univariate Regression		Multivariate Regression	
	Alive	Death				
	n =71	n = 9				
Variables	Number (%)	Number (%)	OR (95% CI)	*P*	AOR (95% CI)	*P*
Age (years)						
0-5	6 (8.5)	5 (55.6)	8.67 (1.82-41.17)	**.007**	9.11 (1.53-54.25)	**.015**
6-15	65 (91.5)	4 (44.4)	Reference		Reference	
Sex						
Male	30 (42.3)	6 (66.7)	2.73 (0.63-11.81)	.18	3.31 (0.64-17.16)	.15
Female	41 (57.7)	3 (33.3)	Reference		Reference	
HIV status						
Positive	14 (19.7)	4 (44.4)	3.26 (0.77-13.73)	.11	2.06 (0.39-10.89)	.40
Negative	57 (80.3)	5 (55.6)	Reference		Reference	

AOR, adjusted odds ratio; OR, odds ratio.
Reference refers to the group the at-risk group is compared in relation with.
For AOR, sex and HIV status were adjusted for age, age and HIV status were adjusted for sex, while age and sex were adjusted for HIV status.

the findings of Panigatti et al[12]in India who had a mean age of 6 years(±3.80).

The most frequent presenting symptoms were cough (98.8%), fever (87.2%), weight loss (70.9%), and night sweats (62.8%). This was consistent with the findings of Aygün et al[8]in Turkey, Nguefack et al[15]in Yaoundé, and Panigatti et al[12]in India. Most children's symptoms lasted for at least 1 month before the consultation. This was similar to the findings of Nguefack et al[15]in Yaoundé. This, however, differs from the findings of Hatherill et al[16]in South Africa where only 43.5% of children had symptoms lasting >2 weeks. The most common physical examination findings were fever (82.6%), chest dullness, crackles or decreased breath sounds (58.1%), and enlarged cervical, axillary, or inguinal lymph nodes (38.4%). This differs from the findings of Panigatti et al[12]in India who had pallor (75.3%), lymphadenopathy (18.3%), hepatomegaly (9.7%), and splenomegaly (6.5%) as the most commonly found physical examination signs. This difference can be explained by the fact that most cases in their study were extrapulmonary TB cases while majority of cases in our study were pulmonary.

Concerning diagnostic modalities, Gene Xpert was positive for 96.2% and smear microscopy was positive for 88.5% of children for whom it was done. Histopathological analysis of biopsy was positive for all the 2 (100%) children for whom it was done. This markedly differs from the findings of Panigatti et al[12]in India, Hatherill et al[16]in South Africa, and Gava et al[13]in Brazil where acid-fast bacilli (AFB) was isolated in only a few specimens. This difference can be explained by the difference in the study designs and the inclusion of presumptive cases of TB in their studies. The difference can also be explained by the fact that in these studies mostly tuberculin skin test, culture for AFB, chest radiography, and histopathology were used for diagnosis while Gene Xpert was rarely used. The high sensitivity of the Gene Xpert and smear microscopy in our study can be attributed to the well-equipped reference TB laboratory with experienced staff. Even though Gene Xpert is expensive, it is more preferable to smear microscopy in our study area due to its reliability and rapid speed of getting results.

Non-cavitating lesions were the most frequent finding on chest x-ray (43.6%). This was consistent with the findings of Nguefack et al[15]in Yaoundé and Hatherill et al[16]in South Africa. This, however, slightly differs from the findings of Yone et al[17]in Yaoundé where the main lesions were cavitations. The difference can be explained by the difference in the study population as Yone et al[17]studied strictly children living with HIV. Majority of the childhood TB cases were pulmonary (96.5%). This is in concordance with the findings of Ramos et al[18]in Ethiopia and Aygün et al[8]in Turkey. This, however, differs from the findings of Panigatti et al[12]in India and Aketi et al[10]in the Democratic Republic of Congo where extra-pulmonary predominated. This difference may be due to the difference in the study designs and the difference in vaccination coverage in the different countries as BCG vaccination reduces the occurrence of extra-pulmonary TB.[3]

As for the outcome, most of the children (76.7%) were cured while few (10.5%) died. The high cure rate and low mortality were similar to the findings of Yone et al[17]in Yaounde, Ramos et al[18]in Ethiopia, Mirutse et al[9]in Ethiopia, and Panigatti et al[12]in India. This, however, differs from the findings of Gava et al[13]in Brazil which had a cure rate of 76.9% and mortality of 3.4%. The high cure rate in our study can be attributed to the availability of the TB treatment center which gives TB medications free as well as the presence of a well-equipped reference TB laboratory for prompt diagnosis and initiation of treatment. It can also be attributed to the distribution of our study population as few children were in an age group (less than 5 years) prone to poor outcomes. The lower mortality in the study of Gava et al[13]can be explained by the fact that presumptive TB cases were included in their study as children who were wrongly classified as TB cases were more likely to have a favorable outcome. The higher mortality rate in our study can also be attributed to the late consultations as parents usually try to suppress symptoms with alternative medications and over-the-counter drugs at the early stages of the disease.

Among all the factors, evaluated age was the only factor which significantly influenced mortality. The risk of death of children

younger than 5 years is increased by 9 times compared to children aged 5-15 years. This is consistent with the findings of Ramos et al[18]in Ethiopia and Mirutse et al[9]in Ethiopia. The increased mortality in younger children can be attributed to the fragility of the immune system and the difficulty of diagnosis in this age group which leads to late initiation of treatment.

With the discussion mentioned earlier, we can conclude that the prevalence of childhood TB was relatively highwhencompared to that found in other studies. The presenting symptoms were consistent with other studies. Gene Xpert, smear microscopy, or histopathology confirmed the diagnosis in a very high proportion of the children compared to findings in other studies. X-ray findings, outcomes, and the age group with increased risk of mortality were consistent with the findings of other studies.

This study, however, has some limitations. Because of its retrospective nature, some information needed for the study was not available in the files. Confounders like the vaccination status of some children could not be gotten. Obtaining the information about the presence of some symptoms was challenging as it is possible that some symptoms were under-reported or reported in a form which was not suitable for the study. There were incomplete files which reduced the study population.

Even with the abovementioned limitations, this study goes a long way in shedding light on the childhood TB situation in our study area.

CONCLUSION

The prevalence of childhood TB in the BRH was 4.5%. The mean age of childhood TB at the BRH was 9.6 (±4.5) years and the sex ratio was 0.8. The most frequent presenting symptoms were cough, fever, weight loss, and night sweats. The most common form of TB was pulmonary. Gene Xpert confirmed the diagnosis in 96.2% of the children, smear microscopy in 88.5%, and histopathological analysis in 100% of biopsied specimens. Non-cavitating lesions were the most frequent chest x-ray findings. We noted a high cure rate and low mortality.Having anage less than 5 years significantly increasedthe risk of mortalityby 9.

Ethics CommitteeApproval: Ethical committee approval was received from the Institutional Review Board (IRB) of the Faculty of Health Sciences of the University of Bamenda (No:2022/0403H/UBa/IRB).

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