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Original article

Clinico-demographic Aspects of Pulmonary and Extrapulmonary Tuberculosis Among Pediatric Patients Admitted to Benghazi Children Hospital, Benghazi 2023

Widyan Alfalah*[1], Yousif Sulaiman[2]

[1]*Department of Internal Medicine, Faculty of Medicine, Benghazi University, Libya.*
[2]*Department of Pediatric, Faculty of Medicine, Benghazi University, Libya.*
***Corresponding Email**. wedyanalfalah@gmail.com*

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In Benghazi Children's Hospital, the infectious department has been a critical topic in the past few years for the frequent admission of tuberculosis cases, which has not been investigated in a descriptive research paper for a time. Our study focused on the clinical features and demographic characteristics of pulmonary and extrapulmonary tuberculosis infection in pediatric patients at our hospital during the period 2020-2023 when the accessibility to healthcare facilities was limited because of Covid-19 pandemic quarantine. Out of the 54 patients included in our case series descriptive study, 38(70.4%) had both pulmonary and extrapulmonary tuberculosis, 13(24.1%) had pulmonary tuberculosis, and 3(5.6%) had extrapulmonary tuberculosis, with the overall most frequent age interval affected is 0-4 years, The majority were female 33(61.1%), the most frequent extrapulmonary tuberculosis was abdominal, which was detected in 25(60.97%)of the patients; out of the 45 samples obtained for GeneXpert assessment 33(73%) were positive, only four patients died during the admission as a result of tuberculosis infection morbid consequences, highlighting the importance of detailed history, clinical examination, laboratory data interpretation, and accurate diagnostic tests in diagnosing tuberculosis infection in pediatric patients. It recommends early diagnosis and management, aiming to raise awareness and inform future research on the disease's nature.

Introduction

According to the WHO, tuberculosis (TB) is the second-leading infectious agent-related cause of death worldwide with burden of more than 10 million people suffering from the disease each year [1]. Of particular importance is the fact that younger children and infants are more susceptible than any other age group to acquire potentially fatal types of tuberculosis (e.g., disseminated tuberculosis, TB meningitis) [2]. Focusing on the clinical picture, epidemiology, course of the disease and its outcome, specifically in this age group, could be quite beneficial in reducing the burden of the TB infection in general.

TB has been known for being commonly prevalent in Libya for decades with recently an estimated 4,000 cases of TB occurring in 2021and incidence of 59 cases for every 100 000 people, however, during the covid-19 pandemic most of the WHO regional Stop TB program and the Health's National TB Control program services have been affected by facing numerous obstacles and limitations through early detection and proper management of TB cases in Libya [3], in addition to after the COVID-19 pandemic, it has been widely recognized by the WHO that an increase in the number of patients with TB was raised worldwide due to the limitations on access to health care facilities caused by quarantine, which makes it a critical period for studying the clinical demographics of a disease such as tuberculosis [1].

Owing on these facts we decided to establish our study focusing on a period of time from 2020 -2023 particularly in the paediatric age group where the detection and diagnosis of the disease is not a quite plane task. It is widely known that children, patients with drug resistant TB, HIV positive individuals, migrants and refugees are found to be the most vulnerable population [4].

In light of this, we focused on describing the presence or absence of these factors in each patient in our study, along with other clinical and demographic aspects of the pulmonary and extrapulmonary tuberculosis, the anti-TB medication regimen used, and investigations done to aid in the diagnosis and evaluation process. We hope that our study will contribute to the development of a more precise and well-defined picture of tuberculosis at Benghazi Children Hospital by the time of the COVID-19 pandemic crisis promoting the process of controlling the tuberculosis infection worldwide.

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Methods

A retrospective descriptive case series study on 54 patients admitted to Benghazi Children Hospital in the period between 2020 and 2023. Data were collected by revising the medical records of the patients aged 0 to 18 years admitted to the infectious department as cases of tuberculosis according to the WHO criteria for the diagnosis of childhood Tuberculosis and by the aim of tuberculin test, GeneXpert, microbiological analysis, or pathology laboratory evidence, previously diagnosed with tuberculosis, or clinically and radiologically goes along with the tuberculosis clinical picture. Patients that didn't meet these criteria was excluded.

The data was collected in 2023 and analyzed by The Statistical Package for the Social Sciences SPSS (Version 25). Qualitative data has been displayed in the form of frequencies and percentages, and we used the mean and the standard deviation for quantitative data.

Results

Clinical and demographical distribution

The total number of patients who met the criteria of diagnosis was 54; patients who did not meet the criteria of the diagnosis have been excluded. Out of the 54 patients included in our study, 33 (61.1%) were females, and 21 (38.9%) were males, with age interval from 0 to 18 years, with a mean age of 7.7 years with a standard deviation of 5.19 years and median age of 8 years. The highest frequency of patients lies in (0-4) interval, 37 (68.5%) of the patients confirmed the history of contact with a tuberculosis-infected individual, 39(72.2%) have received the BCG vaccine in their lives. The residence of 26 (48.1%) patients is Benghazi, while the rest of the patients were from other parts of the country, and patients with Libyan nationality were the majority by frequency of 50 and percent 92.6%.

Based on the criteria used in our hospital to diagnose the tuberculosis infection, 13 (24.1%) of the patients were diagnosed with pulmonary tuberculosis (PTB) without any other systems being confirmed to be involved, three (5.6%) patients with extrapulmonary tuberculosis without any involvement to the pulmonary system, and 38 (70.4%) patients reported to have both pulmonary and extrapulmonary tuberculosis. 37 (68.5%) of the patients were free of any chronic debilitating illness, while four (7.4%) were chronic granulomatous disease patients, five (9.3%) were HIV-positive patients, five (9.3%) were confirmed to have post-COVID-19 pulmonary complications, one patient had a COVID-19 infection by the time of the diagnosis, one patient had sickle cell anemia, and one patient had HCV-positive serology.

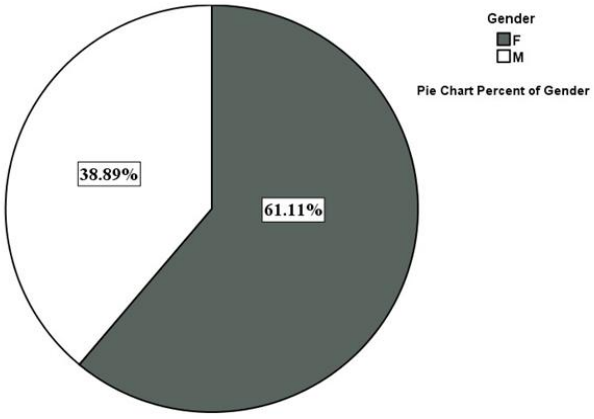

Figure 1. Pie chart of gender percentage.

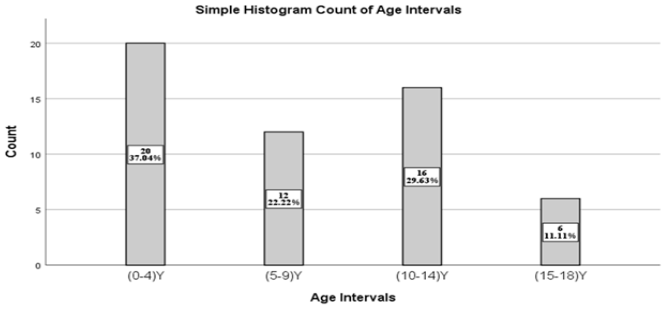

Figure 2. Simple histogram of age intervals

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Table 1. Clinical and demographical distribution.

Tuberculosis form	N (%)	(0-4) Y	(5-9) Y	(10-14) Y	(15-18) Y	Vaccination	residency	nationality
Pulmonary tuberculosis (PTB)	13(24.1%)	8(61.5%)	1(7.7%)	3(23.1%)	1(7.7%)	9(69.2%)	B:7(53.8%) NB:6(46.2%)	LYP:12(92.3% NLYP:1(7.7%)
Extrapulmonary tuberculosis (EPTB)	3(5.6%)	1(33.3%)	1(33.3%)	0	1(33.3%)	3(100%)	B:1(33.3%) NB:2(66.6%)	LYP:3(100%) NLYP:0
PT+EPTB	38(70.4%)	11(28.9%)	10(2.6%)	13(34.2%)	4(10.5%)	27(71.1%)	B:18(47.4%) NB:20(52.6%)	LYP:35(92.1%) NLYP:3(7.9%)

***B**: Benghazi, **NB**: non-Benghazi, **LYP**: Libyan, **NL**: non- Libyan.*

Clinical picture and diagnostic tests

The most common presenting symptom is fever and night sweating, which has been reported in 46(85%) of the patients, followed by cough, which was the complaint of 37 (68%) patients; 34 (63%) patients had weight loss with loss of appetite or decreased feeding; 11 (20.4%) of the patients presented with diarrhea; six (11.1%) patients presented with abdominal pain and vomiting; eight (14.8%) patients had lymphadenopathy as their main complaint; convulsions and abnormal movement were presenting symptoms in 5 (9.3%) patients; headache was presented in four (7.4%) patients; and only three (5.6%) patients complained of restricted joint movement or painful limb. Among patients diagnosed with extrapulmonary tuberculosis, the most common form is abdominal tuberculosis, 25 (60.97%), followed by pleural involvement in 13 (31.7%) patients, lymphadenopathy in 9 (21.95%) patients, seven (17.0%) patients with CNS tuberculosis, five (12.2%) patients with pericardial involvement, and only three (7.3%) patients with musculoskeletal tuberculosis.

As part of the routine investigations, a chest x-ray was done on all the patients. Among patients diagnosed with pulmonary tuberculosis, 46 (85.2%) showed consolidation, five (9.3%) chest x-rays showed miliary tuberculosis, and hilar lymphadenopathy was found in only three (5.9%) chest x-rays. Tests and investigations have been used to help in diagnosis: the tuberculin skin test (TST), GeneXpert, and microbiology evaluation. The TST has been done for 19 (35.2%) patients and was positive only for 12 (63.2%) patients out of those 19. GeneXpert was conducted on samples obtained from 45 (83.3%) patients and was only positive for 33 (73.3%) patients out of all these 45 samples.

Table 2. Microbiological workup.

Sample type	(N)	AFB (+)	AFB (-)
Sputum	15	10/15	5/15
Gastric aspiration	11	5/11	6/11
Paravertebral collection	1	1/1	0
CSF	5	1/5	4/5
LN biopsy	3	2/3	1/3

CSF: cerebrospinal fluid, LN: lymph node, AFB: acid fast bacilli.

Table 3. GeneXpert samples and results.

Sample type	(N)	Positive (+)	Negative (-)
Sputum	22	17/21	5/21
Gastric aspiration	20	13/20	7/20
Paravertebral collection	1	1/1	0
Iliopsoas muscle abscess	1	1/1	0
LN excisional biopsy	1	1/1	0

Laboratory findings and Radiological evaluation

Complete blood count done for all the 54 patients; anemia found in 43 (79.6%) of the patients while leukocytosis was found in 19 (35.2%) of the patients. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were done on all of the 54 patients as part of the routine investigations. CRP was found to be raised in 30 (55.6%) of the patients, and ESR was found to be raised in 20 (37%) patients. Abdominal ultrasonography was used for case evaluation in 14 (25.9%) patients; all showed findings related to abdominal tuberculosis except for one, who was free of any relatable findings. Computed tomography scan (CT scan) used for evaluation for 8 (14.8%) patients abdominal scan, 13 (24.1%) patient's chest scan, and two (3.7%) patient's spine CT scans. Magnetic resonance imaging (MRI) has been used in the evaluation of

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three (5.6%) patients: two MRI spines and one MRI brain. All these imaging techniques showed pathology goes with the diagnosis of tuberculosis.

Treatment regimen used during Hospital admission and outcome:
The most commonly used regimen was Isoniazid (H) + Rifampicin (R) + Pyrazinamide (Z) + Ethambutol (E), HRZE, which has been used in the treatment of 47 (87%) patients, while second-line anti-tuberculosis drugs have been added to the treatment regimen of four (7.4%) patients. Rifampicin resistance has been reported in five (9.3%) patients; four (80%) of them received second-line anti-tuberculosis treatment, and one of them lost the follow-up. Prednisolone has been used in the treatment of 12 (22.2%) patients whenever central nervous system or pericardial involvement has been suspected or confirmed. Only four (7.4%) patients out of all 54 patients have passed away during the admission period because of the tuberculosis infection and its morbid consequences; the rest of the patients were discharged from the hospital to be on a regular follow-up with the infectious clinic.

Discussion
Based on our observations, the most frequent age group affected by tuberculosis (TB) infection is between 0 and 4 years, suggesting that children's immature immune systems make them more susceptible to tuberculosis infection, with a higher risk of progression to active disease compared to adults, particularly for children under 2years of age specifically and under 5 years of age in general. [5,6] This observation essentially apprises us in the first place to focus on the pediatric age group. Regarding patient characteristics and disease epidemiology, our results showed a female predominance (61.1%), consistent with the findings of a study conducted in southwestern Iran within the same age group. However, this does not correspond with the WHO and other studies, which suggest that TB infection is more frequent among males in all age groups. [7-12] Further investigation is required to explain this variation. 68.7% of our patients had close contact with known cases of TB; this emphasizes the top priority of tuberculosis prevention and control programs, which is the importance of identifying and treating all active TB cases, with contact investigations being a crucial step. [13] Benghazi Children's Hospital serves the vast eastern Libyan region; thus, only 48% were Benghazi city residents, while the rest of the patients were from other suburban and rural areas. 92% of patients were Libyan, primarily due to unregistered non-Libyan patients and unidentifiable concerns among international patients who may choose to leave the country or visit other facilities. [14]
Numerous studies have evaluated the effectiveness of the BCG vaccine in preventing pulmonary tuberculosis and demonstrated significant variations in preventive efficacy based on a variety of factors, including an effectiveness rate ranging from 16 to 73% (protection against tuberculous meningitis and miliary tuberculosis was more than 50% in all studies, protection against pulmonary tuberculosis varied from 10 to 66%) [15]. Because our study excluded non-TB-infected BCG-vaccinated children, we were unable to draw any conclusions regarding the efficacy of the BCG vaccine. Nevertheless, the percentage of vaccinated patients observed in our study was (72.2%), which is still less than the 90% observed in a study conducted in Turkey [16]. This may serve as an indicator that offers valuable insights into the various factors affecting BCG vaccine efficacy, which are known to be influenced by numerous elements, including administration methods, demographics of the vaccinated population, and environmental conditions [17].
Immunocompromised patients are at a higher risk of developing active TB infection [18], which accounts for our observations of 9.3% of patients with chronic granulomatous disease and 9.3% of HIV-positive patients. In addition to the fact that in case of HIV, tuberculosis is considered to be the leading cause of death [19]. Children with TB are more likely to have extrapulmonary tuberculosis (EPTB) and disease progression than adults. Infants have a high rate of morbidity and mortality due to the immaturity of the immune system [5] and lymphohematogenous dissemination [16]. 75.9% of our patients had EPTB; this is considered to be higher than the observations of many studies from different countries (UK 38.11%, India 17.68%, Italy 30.87%, Turkey 30.50%, USA 24.52% and China 46%) [20- 25]. This may be due to the different design and criteria of each; however, at this point of discussion to have more solid explanation, we recommend more future studies on EPTB among children in Libya. Abdominal tuberculosis, accounting for only 12% of pediatric extrapulmonary tuberculosis, is often underestimated due to nonspecific presentation, limited availability of imaging techniques, and microbiological confirmation in high TB burden settings [26]. Although abdominal tuberculosis was the most frequent form of EPTB in our study, followed by pleural and TB lymphadenitis, this is similar to the results of a study conducted in Pakistan in 2016 [27], and does not match the fact that tuberculosis lymphadenitis is the most common form of EPTB [28].
Tuberculosis in children frequently presents with nonspecific symptoms, such as fatigue, night sweats, evening fever, weight loss, and cough. [29] This is consistent with our observations that fever and night sweating were the most frequent presentations, followed by cough and weight loss. Owing to these nonspecific presentations, it can be difficult to diagnose the condition accurately in a timely manner before

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it progresses and causes difficult-to-manage consequences. It is well known that in case of primary pulmonary TB in children, the most prevalent finding on CXR is consolidation (70 %) without significant lobar predilection, and the well-known radiologic hallmark is hilar and/or mediastinal lymphadenopathy (46%–50%), which is considered to be more frequent in children than in adults. [30] this correlate with 85.2% parenchymal consolidation out of all CXR performed to our patients, despite hilar LAP considered to be a hallmark only found in 5.9% of our patients. 9.3% showed the typical miliary mottling (homogenously distributed, discrete, uniform 1- 2 mm in size millet-shaped lesions in all lung zones), known that these findings not usually found in early disease in case of the miliary TB according to this Contrast-enhanced CT (CECT) is highly recommended for further evaluation in this case [31], referring to the advantages of these advanced imaging techniques all the CT-scans and MRI that been used for evaluation in our study were positive with findings goes with tuberculosis, also the ultrasonography was quite beneficial in the process of evaluation.

GeneXpert is well-known for its 100% specificity and variable sensitivity depending on the sample type [32], the most sensitive is sputum followed by gastric aspiration [33], in view of these facts in our study we found that GeneXpert was 73.3% positive out of 45 samples, Although TST cause false positive in a previously BCG-vaccinated population[34], it was also helpful in situations where GeneXpert was negative or in cases necessitated the use of tests other than GeneXpert for diagnosis. Furthermore, we noted that AFB was not easily detected each time a microbiological study was used in the diagnosis. Regarding laboratory data, anemia is one of the risk factors for mortality in patients with tuberculosis, which is the most frequent finding seen in hematological parameters in tuberculosis infection [35], which strongly agrees with our observations where anemia was found in 79.6% of all 54 patients. In addition to leukocytosis, which is considered a fundamental characteristic of TB [35], only 35.2% of our patients had leukocytosis, and more than half of the patients had elevated CRP, while ESR was elevated in more than one-third of the patients. Together gives a hint about such aberrant hematological findings that are inexplicably present and should elicit a high suspicion of tuberculosis.

During the admission period and after the establishment of the diagnosis, we found that the most frequent regimen used was the inclusion of Ethambutol, Isoniazid, Pyrazinamide, and Rifampicin, fulfilling WHO recommendations regarding antituberculosis management [36], taking into consideration the circumstances of the current increased incidence of drug-resistant forms of tuberculosis, and the daily challenges facing clinicians related to prescription of less effective and toxic second-line drugs [37], Rifampicin MTB resistance was detected in five of our patients when the second-line antituberculosis was involved in the treatment protocol. In general, the retrospective methodology and very small patient population are considered factors contributing to the limitations of our observations. However, we still believe that our research is significant because it adds to the data on pediatric tuberculosis in our country and our nation, so it could be a great help in future plans for controlling and dealing with tuberculosis.

Conclusions

Our study briefly provide valuable data regarding tuberculosis infection in Benghazi Children Hospital by the time of the COVID-19 pandemic, drawing the conclusion that due to the unspecific presentation, variable diagnostic test results, and different radiological findings when it comes to the process of the diagnosis of tuberculosis in pediatric patients, we strongly recommend a proper detailed history, full clinical examination, laboratory data interpretation, and radiology aid with accurate diagnostic tests all in combination should be assessed to reach an early diagnosis to establish the management as soon as possible. We hope that our data are shared in the awareness and understanding of the nature of tuberculosis infection, in addition to providing material that could be beneficial and helpful for future studies and research.

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المستخلص

في مستشفى الأطفال ببنغازي، كان قسم الأمراض المعدية موضوعًا بالغ الأهمية في السنوات القليلة الماضية بسبب القبول المتكرر لحالات السل، وهو ما لم يتم التحقيق فيه في ورقة بحثية وصفية لفترة من الوقت. ركزت دراستنا على السمات السريرية والخصائص الديموغرافية لعدوى السل الرئوي وغير الرئوي لدى مرضى الأطفال في مستشفانا خلال الفترة 2020-2023 عندما كان الوصول إلى مرافق الرعاية الصحية محدودًا بسبب الحجر الصحي بسبب جائحة كوفيد-19. من بين 54 مريضًا مدرجين في دراستنا الوصفية لسلسلة الحالات، كان 38 (70.4٪) مصابين بالسل الرئوي وغير الرئوي، وكان 13 (24.1٪) مصابين بالسل الرئوي، وكان 3 (5.6٪) مصابين بالسل خارج الرئة، وكانت الفترة العمرية الأكثر شيوعًا المتأثرة هي 0-4 سنوات، وكانت الأغلبية من الإناث 33 (61.1٪)، وكان السل خارج الرئة الأكثر شيوعًا هو البطن، والذي تم اكتشافه في 25 (60.97٪) من المرضى؛ من بين 45 عينة تم الحصول عليها لتقييمGeneXpert ، كانت 33 (73٪) إيجابية، توفي أربعة مرضى فقط أثناء القبول نتيجة لعواقب مرضية لعدوى السل، مما يسلط الضوء على أهمية التاريخ التفصيلي والفحص السريري وتفسير البيانات المعملية والاختبارات التشخيصية الدقيقة في تشخيص عدوى السل لدى مرضى الأطفال. ويوصي بالتشخيص المبكر والإدارة، بهدف زيادة الوعي وإعلام البحوث المستقبلية بطبيعة المرض.

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