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ORIGINAL RESEARCH

Pediatric Tuberculosis at Moulay Youssef University Hospital – Morocco.

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ABSTRACT
Background: There are few studies on presentations, treatment and outcomes of pediatric tuberculosis in Morocco. This study aimed to describe clinico-epidemiological profiles, laboratory findings, treatment and outcomes of pediatric tuberculosis (TB) in a tertiary care hospital in Morocco.
Materials and Methods: This is a prospective, descriptive study undertaken in children diagnosed with TB between June 2011 and May 2012. Clinico-pidemiological profiles, laboratory findings, treatment and outcome of patients was recorded. Statistical significance of category variables was evaluated. Analysis was done on SPSS package. Results were expressed as rates and proportions. Chi square test was used to test for statistical significance.
Results: 53 children aged 2 to 16 years (mean age of 9±3.2) with TB diagnosis were enrolled in our study. 33 (62%) of patients were female. Common symptoms were fever, cough, chest pain, dyspnea, decreased appetite and weight loss. The types of TB were: pulmonary TB (32, 60%), and extrapulmonary TB (21, 39.6%). The sites of pediatric extrapulmonary tuberculosis (EPTB) were: lymph nodes (7, 13.2%), peritoneal (6, 11.3%), meningeal (4, 7.5%) and osteoarticular (4, 7.5%). 24 (45,3%) of the patients had positive Calmette-Guérin vaccine scar, and 42(79.2%) of the patients had a positive tuberculin skin test. An adult TB contact was identified in 19 (35.8%) of the cases. On direct microscopy, acid-fast bacilli were found in 3 (5.6%) patients and positive culture for Mycobacterium tuberculosis was found in 2 (3.7%). Drug mono- or multiresistance was not detected.
Conclusion: Paediatric TB in both pulmonary and extrapulmonary forms is a challenging diagnosis, and is a common occurrence in our setting. Diagnosis was based on a combination of epidemiological and clinical suspicion supported by results of various investigations.

KEY WORDS
Pediatric; Tuberculosis; Pulmonary, Lymph nodes.

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INTRODUCTION

World Health Organization (WHO) reports that about two billion i.e. nearly one third of the world's population is currently infected with mycobacterium tuberculosis. Of the 8.6 million incident cases, an estimated 0.53 million (6%) were children. The global number of new TB case notifications among children (< 15 years) is estimated at 349000 in 2012 [1].

Pediatric TB is important for public health professionals since it is an indicator of the recent and ongoing transmission of TB in the community since it develops as a result of dissemina¬tion from adults and adolescents with

cavitary lung disease, and it represents a major unrecognized cause of disease and death during childhood in endemic countries [2-4]. It is estimated that childhood TB constitutes 10–20% of all TB in high-burden countries, accounting for 8–20% of TB-related deaths [5]. Contact investigations of pediatric TB patients may lead to improved case-finding among adult patients [6]. Several studies have described the pediatric TB epidemic in high HIV/TB coinfection settings such as sub-Saharan Africa [7, 8].

Moreover, diagnosis of tuberculosis (TB) is particularly challenging in children [9]. The symptoms of pediatric TB infection are often non-specific or absent. Adequate specimens for diagnosis are usually difficult to obtain in children younger than 8 years due to a paucity of sputum [10]. Even in tertiary care centers, a definitive diagnosis is established in no more than 30% to 40% of patients [11]. For this reason, the diagnosis is usually based on a history of contact, positive tuberculin skin test, and characteristic radiographic abnormalities [12, 13].

Data on the incidence and clinical course of pediatric tuberculosis are lacking and limited from low-income countries like Morocco, they are mostly reported from low-burden countries [14].

This study was performed in our referral hospital for TB in Rabat to describe the clinico-epidemiological profile, diagnostic processes and treatment outcomes of pediatric TB.

Materials and methods

Study setting

This is a prospective and descriptive study that was conducted between June 2011 and May 2012 at Moulay Youssef University Hospital (HMY) which is a tertiary care hospital affiliated to Rabat Medical College. HMY is the only referral center for the north of Morocco for the treatment of pediatric TB. In 1991, DOTS (Directly Observed Treatment, Short course) program was started in our hospital under the National TB Program of Morocco. Ethical clearance was obtained from ethical committee of Rabat Medical College and permission to record medical data was obtained from the medical superintendent of HMY.

Study population

Analysis included only persons < 15 years, dignosed as TB and admitted for further investigation and treatment of TB. Inclusion criteria were children presenting with either fever and/or cough for ≥2 weeks, with or without weight loss or no weight gain, or showing neurological symptoms like irritability, refusal to feed, headache, vomiting, or altered sensorium and suspected to have TB meningitis. Exclusion criteria included the inability to obtain informed consent or permission for HIV testing, children on TB treatment or prophylaxis for more than 7 days, and children for whom followup was difficult.

The following patient data were analysed for this study: demographic data, presenting symptoms, household contact with an active case of pulmonary TB, clinical features, history of BCG vaccination and/or presence of BCG scar (at least four millimeters in size), Mantoux test, bacteriological results, drug susceptibility, tests for HIV infection. An investigation for a source case/contact in families was conducted by local TB control officials.

TB was defined as a child with either confirmed or probable. Confirmed TB (At least 1 of the signs and symptoms are suggestive of tuberculosis and microbiological confirmation is obtained), probable TB (definition derived from international consensus guidelines [15].

Diagnostic procedures

The diagnosis of TB was performed according to the 2011 guidelines of National TB Program of Morocco through clinical findings, history of exposure to a positive source case, a positive tuberculin skin test (TST), microbiological results, radiological findings, and histopathological findings. For the purpose of our analysis, the type of TB was classified as isolated pulmonary TB, extra-pulmonary TB, pulmonary TB with extra-pulmonary TB (only one extrapulmonary site), disseminated (pathology in more than two sites) and miliary TB.

Treatment protocols

The basic treatment and standard anti-TB regimens for children (<35 kg) were provided according to the guidelines of the Moroccan TB Program. Treatment of most forms of PTB and extrapulmonary TB (EPTB) consists of a 6-month, short-course chemotherapy regimen with 3 drugs : Isoniazid [10 mg/kg (10-15 mg/kg)], Rifampicin [15 mg/kg (10-20 mg/kg)],, and Pyrazinamide [35 mg/kg (30-40 mg/kg)], in the initial 2-month intensive phase, followed by 2 drugs (INH and RFP) in the 4-month continuation phase.

Treatment of neuromeningitis and osteoarticular TB consists of a 6-month, short-course chemotherapy regimen with 4 drugs : Isoniazid [10 mg/kg (10-15 mg/kg)], Rifampicin [15 mg/kg (10-20 mg/kg)], Ethambutol [20 mg/kg (10-20 mg/kg)], and Pyrazinamide [35 mg/kg (30-40 mg/kg)], in the initial 2-month intensive phase, followed by 2 drugs (INH and RFP) in the 10-month continuation phase.

Statistical Analyses

Data was entered and analysed using the Statistical Package for the Social Sciences for Windows (Version 11.0; SPSS, Inc., Chicago, IL, USA). Data was presented as rates and proportions. Statistical significance of difference in proportions was tested using Chi Square Test and a p-value less than 0.05 was considered as significant.

RESULTS

Clinical findings

A total of 53 children hospitalized with TB were enrolled in our study between June 2011 and May 2012. The mean age of the patients was 9±3,2 years, and the age range was 2 years to 15. 20 (38%) patients were male, 33 (62%) was female, with a sex ratio of 2/3.3. The most common presenting symptoms were fever, cough, chest pain, weight loss and loss of appetite as shown in table 1. Distribution of the cases by clinical form and microbiological data are shown in Table2. Histopathological evidence of

granulomatous inflammation and caseous necrosis con¬sistent with TB were found in the patients with abdominal TB, and lymphadenitis. Intrathoracic TB was noted in 6 (11%) children who were aged less than 5 years and in 18 (34%) children aged between 6 to 10 years. Extrathoracic TB were seen in 3(6%), and 9(17%) patients, respectively, in the same two groups (Table 2). 26 (49%) patients had a household TB contact, 57% (15) of these patients had thoracic TB and 43% (11) extrathoracic TB.

Complaint	N (%)
Fever	42 (79%)
Cough	34 (64%)
Lymph node swelling	5 (9%)
Chest pain	14 (26%)
Loss/decreased appetite	39 (74%)
Breathlessness	11 (20%)
Weight loss	43 (81%)
Hemoptysis	7 (13%)
Diarrhea	7 (13%)
Abdomen pain	3 (5%)

Table 1 Presenting symptoms of the children diagnosed as Tuberculosis

Characteristic	IPT N (%)	EPT N (%)
Age group (years; mean)		
2-5	6(11%)	3(6%)
6-10	18(34%)	9(17%)
11-15	8(15%)	9(17%)
Gender		
Male	12(22%)	8(15%)
Female	20(38%)	13(24)
Location		
Rural	8(15%)	4(7.5%)
Urban	24(45%)	17(32%)
BCG vaccinated		
No	23(43%)	15(28%)
Yes	9(17%)	6(11%)
Time to hospital visit, days		
0–30	22(42%)	16(30%)
>30	10(18%)	5(9%)
Contact history at home		
Yes	15(28%)	11(21%)
No	17(32%)	10(18%)

Table 2 Patient Characteristics According to TB Type

Laboratory findings and other investigations

The most common laboratory findings were increased leukocytosis (29/53, 56.9%), C-reactive protein (28/53, 54.9%), and erythrocyte sedimentation rate (31/53, 60.8%). Lymphopenia was common (19/53, 35.8%). Hyponatremia was also seen (7/53, 13.2%). According to CXR and CT scans, the most common radiological findings were mediastinal lymphadenopathy (37/53, 72.5%), pneumonic infiltration and consolidation (28/53, 54.9%), pleural effusion (7/53, 13.7%), and miliary pattern (5/53, 9.8%).

BCG vaccination

48 (90.5 %) patients of our cohort had been vaccinated. BCG scar was noted in 24(50%) cases.

Tuberculin skin test

All patients underwent a TST, 42 (79%) demonstrated indurations >10 mm upon tuberculin testing.

Description of pulmonary TB cases

The most common symptoms of PTB were cough (64%%) followed by chest pain (26%). 20% had dyspnea, and 13% had hemoptysis. 81% had weight loss, and 79% presented fever and night sweats.

Description of extrapulmonary TB cases

There were 21 cases of extrapulmonary tuberculosis. 7 patients had TB lymphadenitis. 3 of them was localized in the cervical region and along the axillary line in the other. Histopathological findings of fine needle aspiration biopsy samples confirmed the diagnosis of TB. 6 patients had peritoneal TB. In these patients, examination of biopsy samples revealed granulomatous reaction and pathological findings consistent with tuberculosis. 4 cases of central nervous system TB Cerebrospinal fluid analysis of these patients revealed low chloride and glucose levels, turbid appearance, high pressure and markedly elevated protein. All of them had pleocytosis with lymphocytic predominance. Acid-fast stain of cere-brospinal fluid for tuberculosis bacilli was negative for all samples, and bacterial cultures yielded no growth. In all cases, AFB and mycobacterial culture of gastric aspirate sample were negative. In all patients, consolidation and infiltration were observed on CXR. Four last cases had osteoarticular TB.

Treatment

45 cases were treated with 3 drugs (Isoniazid, Rifampycin, and Pyrazinamid). 8 cases with neumenigitis or osteoarticular TB received a 4 drugs regimen with ethambutol as the additional agent. 15 of the cases were also given steroid therapy. All patients were followed daily during hospitalisation and once a month thereafter. All patients responded well to the treatment.

Source identification

Half of the patients had a positive history of exposure to adult TB. In addition, seven adult cases was detected by contact tracing.

Clinical presentation	N (%)	Positive TST	BCG scar	Positive AFB	Positive culture
Intrapulmonary TB	**32 (60%)**	**28 (53%)**	**15 (28%)**	**3 (6%)**	**2 (4%)**
Extrapulmonary TB	**21 (40%)**	**14 (27%)**	**9(17%)**	**1 (2%)**	**1 (2%)**
Abdominal TB	6	5	3	0	**0**
TB lymphadenitis	7	3	3	1	1
TB meningitis	4	3	2	0	0
Osteoarticular TB	4	3	1	0	0
Total	**53 (100%)**	**42 (79%)**	**24 (45%)**	**4 (7.5%)**	**3 (6%)**

Table 3 Distribution of the Cases and Diagnostic Findings by Clinical Form of the Disease

n/n denotes number of patients with positive result/number of patients with available data.

DISCUSSION

Tuberculosis is a major health problem in the developing world. It's still among the top 10 causes of death among children worldwide. Of the one million estimated cases of TB in children worldwide, three quarters occur in the 22 high-burden countries [1]. However, pediatric TB is given low priority in most national health programs and is also neglected in this epidemic. In Morocco, over 26,000 new cases of TB are reported annually [16]. We have a national TB programme, and a nation-wide network of specialized healthcare facilities to combat against the disease. In high-burden countries a considerable proportion of TB patients are children and TB related morbidity and mortality is high among children [17]. The high prevalence of childhood TB is an indication of the continued dissemination of the disease.

Clinical and radiological findings of childhood tuberculosis are not specific and different from adults. In addition, sampling, confirmation and final diagnosis pose a challenge [18, 19]. Sputum samples are difficult to collect from children and sputum-smear microscopy or culture yields are lower [20-22]. Moreover, acute tuberculosis may present in the form of acute pneumonia in children, which is quite difficult to differentiate clinically and radiologically from other pathogens [9, 23].

Common symptoms in our study were fever, cough, chest pain, decreased appetite and weignt loss. Though distribution of all forms of TB was similar across all age groups, there was slight peak for pulmonary TB among children aged less than five years and a slight trough for extra-pulmonary TB after 10 years of age ($P<0.05$). Most common extra-pulmonary site were meninges, peritoneum, cervical lymph nodes (mainly), and bone and joints. For the diagnosis of thoracic TB, chest radiograph, mantoux and BCG tests were done while extrathoracic TB was diagnosed using respectivly diagnostic procedures. Our analysis about the diagnostic procedures revealed that there was no single diagnostic procedure which could be used as a gold standard test. Most children underwent many diagnostic procedures before a final diagnosis of TB was made.

There is a difficulty in interpreting a positive TST in our setting where universal BCG vaccination is done during neonatal period. TST is not specific and sensitive enough, since BCG immunization can cause false positive results. Though negative TST does not rule out TB, as long as malnutrition and miliary tuberculosis may result in false negative results. A positive test is used for the diagnosis of latent tuberculosis infection (LTBI), it may also be a useful diagnostic tool in a resource-limited setting like ours [24].

In our study radiological findings were noted as mediastinal lymphadenopathy (63.6%), primary focus-calcification (56.8%), miliary pattern (20.4%), pneumonic infiltration (15.9%) and cavitary lesion (9%) among pediatric patients. Mycobacterial culture is more sensitive than direct microscopy. In this study, culture was positive while smear was negative in 2(4%) of patients. In most previous studies from other geographical regions, positive culture rates ranging between 30 and 40% were reported [8, 9, 25, 26].

The most important approach in the fight against the disease is detection, identification and treatment of the source cases, as well as BCG vaccination soon after birth [9, 27, 28]. In our country, all infants routinely receive BCG vaccination at birth. However, 9.5% of infants in our cohort skipped vaccination due to sociocultural issues or because they are living in rural areas and far from health centers. Like similar studies, only about half of these children had BCG scar [9, 29]. This rate of vaccination among diseased children suggests that lack of vaccination may be a contributing factor for the development of the disease, although protection rate of BCG vaccination is controversial [9, 29]. In our study, the proportion of EPTB in the non-BCG vaccinated group was higher than in the BCG vaccinated group (43% vs 17%), the proportion of PTB in the non-BCG vaccinated group was also higher than in the BCG vaccinated group (28% vs 11%). The difference was not statistically significant ($P=0.06$).

In this study, 27 of the 53 patients (52.9%) had contact with an adult case of TB. High TB contact rate found on active screening in this study suggests that adults may not present with typical TB symptoms. Corresponding figures for contact rates ranged from 22.6 to 59% in previous studies [9, 29, 30]. Thus, many adults would have been missed if not traced.

Few studies have suggested about increasing trends of extra-pulmonary manifestations among children as well as adults [2, 31, 32]. Most common extra-pulmonary site in our setting was lymph nodes (cervical and axillary) similar to studies reported previously [2, 32, 33]. The second common site was the peritoneum.

EPTB was diagnosed mainly by fine needle aspiration cytology (FNAC) and biopsy. These findings emphasize about the diagnostic difficulties faced by physicians in resource-limited settings. Such findings have been reported from other countries as well [2, 34-36].

Treatment of most forms of PTB and EPTB in our practice consists of a 6-month, short-course chemotherapy regimen with 3 drugs : Isoniazid, Rifampicin, and Pyrazinamide, in the initial 2-month intensive phase, followed by 2 drugs (INH and RFP) in the 4-month continuation phase.Treatment of neuromeningitis and osteoarticular TB consists of a 6-month, short-course chemotherapy regimen with 4 drugs (+ Etb) in the initial 2-month intensive phase, followed by 2 drugs (INH and RFP) in the 10-month continuation phase. Current recommendations advise extension of treatment to 9–12 months for miliary, meningeal, bone and joint, or disseminated TB [38].

Current WHO guidelines advise that all children <5 years of age who are in close contact with a sputum smear–positive index patient should be actively traced, screened for TB, and provided preventive chemotherapy after active TB has been excluded [37].

Further studies on the diagnosis and management of pediatric tuberculosis with bigger cohorts in different centers in Morocco are warranted in this age group.

CONCLUSION

In summary, pediatric tuberculosis is still an important

health problem in Morroco. Focusing on active contact tracing among all household contacts of index cases may be helpful in identification and controlling the disease. Refinement of existing tools and development and testing of new tools are urgently required to improve diagnosis and treatment of TB in children. Adopting a more suspicious and proactive approach in this particular age group would prevent delay in diagnosis and disease related complications.

ABBREVIATION

TB	Tuberculosis
AFB	Acid-fast bacilli
BCG	Bacillus Calmette-Guérin vaccine
TST	Tuberculin skin test

SOURCE OF SUPPORT
Declared none.

COMPETING INTERESTS
The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS
The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

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