Original Article

Pediatric tuberculosis in Iran: a review of 10-years study in an Iranian referral hospital

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Abstract. *Introduction:* Reductions in global tuberculosis incidence are considered as one of the End TB Strategy goal. The diagnosis of tuberculosis (TB) in children is challenging due to insufficient specimen material and the scarcity of bacilli in specimens. The purpose of this study was to evaluate the prevalence, characteristics, clinical profiles, laboratory findings and treatment outcomes of children infected with TB in an Iranian referral hospital during a 10-years period. *Methods:* This study was a retrospective analysis of the medical records of 90 children (≤15 years) with a diagnosis of tuberculosis who were admitted to Children's Medical Center Hospital, Tehran, Iran, between March 2006 and March 2016. The patients' information such as demographic, clinical manifestations, laboratory, radiological and histological tests results, and treatment outcomes were extracted from medical records and were analyzed. *Results:* The total prevalence of TB was about 56.6 per 100,000 admitted patients. Most of the patients were between 5 to 12 yearsTwenty-two percent had the history of TB in their family. Underlying diseases were identified in 30 cases (33%). Thirty-four cases (38%) had pulmonary TB (PTB), 35 cases (39%) had extrapulmonary TB (EPTB), while disseminated TB (DTB) was found in 21 cases (23%). Distribution of DTB in males was higher than in females (36% vs. 6%). In patients < 1 year, DTB was the most frequent type (48 %); however, in patients > 1 year both PTB and EPTB had similar distributions (42%) and were more frequent than DTB (16%). In overall, a mortality of 10% was reported. *Conclusions:* The total prevalence rate of TB in our study was 56.6 per 100,000 admitted patients. Since the mortality rate was higher in infants, children with DTB and children with underlying diseases, early detection and treatment of these patients will help to reduce the mortality rate of TB disease. (www.actabiomedica.it)

Key words: Children, Tuberculosis, Iran

Introduction

Tuberculosis (TB) is considered as the second fatal infectious disease after acquired immune deficiency syndrome (HIV/AIDS) (1). According to the world health organization's (WHO) estimation, approximately 1 million children infected with TB during 2015 and its mortality rate is more than 136,000 deaths annually (2). TB is more prevalent in developing countries such as Iran; however, Bacille Calmette-Guerin (BCG) vaccine has been given to children after birth or at first contact with the health services (3,4). The incidence of TB in Iran was 13 per 100,000 populations and 4% of the reported cases were children less than 14 years (5). The highest risk of death in TB infected children is found in those younger than 5 years, HIV infected, those with recent exposure to TB and immnuocompromised children (6,7).

TB in children usually reflects recent transmission from an infectious adult with pulmonary TB (2), so control of childhood TB depends on both child and family (3). Even though the importance of children in transmission of TB in the community is lower than adults, postponement in the diagnosis and treatment of infected child may form a contagious reservoir for TB spread and can increase the mortality rate of the disease (2,8).

There are some differences between pediatric TB and TB in adults. The short incubation period of disease, low rate of acid fast bacilli in specimens, lack of cavitary lesions due to the immature immune responses, less productive and forceful cough, different clinical and radiographic manifestations and finally, and type of the TB (children tends to be extra pulmonary disease) are considered as the most important factors in children which differentiate pediatric TB from adults TB in (3).

The diagnosis of tuberculosis in children is difficult to confirm microbiologically because the bacillary load is low and young children are unable to expectorate sputum and it is hard to obtain gastric aspirates, so the yield of such samples are little (9). Therefore, diagnosis of pediatric TB is usually on the basis of a combination of clinical presentations, chest radiography (CXR) and computed tomography (CT) scan, contact history, tuberculin skin test (TST) and bacteriologic examination (10).

The aim of this study was to describe the prevalence, characteristics, clinical profiles, and treatment outcomes of the pediatric patients with TB in Iran during a 10 years interval.

Material and methods

This was a retrospective study on patients suffering from TB admitted to Children Medical Center Hospital, a referral hospital of children in Tehran, Iran during March 2006 to March 2016. All children younger than 15 years that were diagnosed with TB were included in the study. TB was defined based on the following criteria: (1) presence of clinical symptoms (chronic cough, weight loss, prolonged fever and respiratory distress), (2) manifestations on the chest radiography (hilar lymphadenopathy, pneumonia, plural effusion, collapse consolidation, cavity in the lung), (3) history of TB contact, (4) the TST (using 5 TU), (5) Acid fast staining of biological fluids (sputum, gastric aspirates etc.), (6) culture (7) laboratory tests (hematology and plasma biochemistry) and (8) PCR test. Any child that had 3 or more of the mentioned criteria was defined as TB infected (8). Results of TST were read at 48–72 hours after injection and transverse diameters of ≥10 mm and ≥5 mm were considered positive in HIV-uninfected and HIV-infected children, respectively. Treatment outcomes of childhood TB: the outcomes of treatment were reported as either cured, or died (10).

Types of TB disease were defined as follow:

Pulmonary tuberculosis (PTB): Patients with disease restricted to the lung parenchyma, pleura, and intrathoracic lymph nodes were classified as having PTB (10).

Extra pulmonary tuberculosis (EPTB): Patients with both pulmonary and extra pulmonary (organs or tissues outside the thorax) infection were considered to have EPTB (10).

Disseminated TB (DTB): Patients that *M .tuberculosis* was isolated from their blood or bone marrow, from liver specimen or from specimens from > 2 non-contiguous organs were considered to have DTB (11).

Statistical analysis

Descriptive statistics were used to summarize all demographic data of patients, laboratory and imaging findings. A chi-square test was used to evaluate the association between types of TB disease and sex and age of patients. All statistical analyses were done using statistical packages SPSS 16.0 (SPSS Inc. Chicago, IL). A *P* value ≤ 0.05 was considered statistically significant.

Results

During a 10 years period, a total of 90 children with TB were identified and included in the study. The total prevalence of TB was about 56.6 per 100,000 admitted patients. The annual prevalence of pediatric TB was shown in Figure 1.

The prevalence rates in 2007 and 2010 were the highest (85.3 and 84.3 per 100,000 admitted patients,

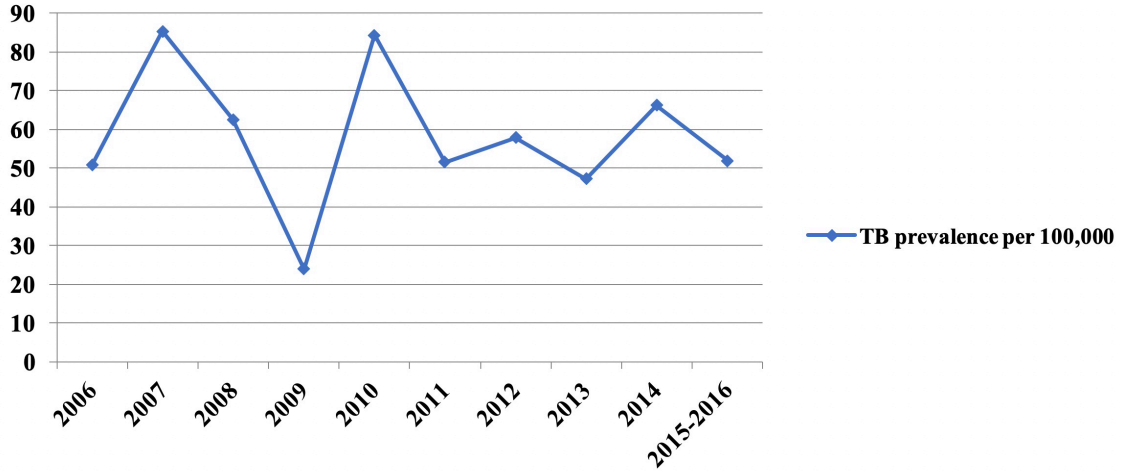

Figure 1. The prevalence of childhood TB in an Iranian referral hospital from 2006-2016

respectively) and the lowest prevalence was seen in 2009 (23.92 per 100,000 admitted patients). Baseline characteristics of the patients are shown in Table 1.

The age of the patients ranged from 4 month to 15 years with a median age of 4.25 years (interquartile range [IQR], 1.1–9 years). Most of the patients (42%) were between 5 to 12 years. Fifty-five cases (61%) were male and the male to female ratio was about 1.6. Among the patients, 11 cases (12%) were Afghan and others were Iranian (79%). Twenty children (22%) had the history of TB in their family.

Underlying diseases were identified in 30 cases (33%) including: BCGosis (11%), chronic granulomatous disease (CGD) (8%) , HIV (7%), defects of the IL-12/IFN-γ Axis (5.5%), leukocyte adhesion deficiency-1 (LAD-1) (2%), severe combined immunodeficiency (SCID) (2%), common variable immune deficiency (CVID) (1%) , Bernard Soulier syndrome (1%), down syndrome (1%), hepatitis C (1%), trisomy 9 (1%) and cystic fibrosis (1%) (Table1). Three patients were diagnosed with both BCGosis had defects in the IL-12/IFN-γ Axis, one patient had HIV and hepatitis C co-infection and one patient was infected with both HIV and cystic fibrosis.

Of the total 90 cases, 34 cases (38%) had PTB, 35 cases (39%) had EPTB and 21 cases (23%) were diagnosed as DTB. The most frequent form for EPTB was skeletal TB with 13 cases (37%), while endocarditis TB was the least frequent form and was seen in only 1 patient (2%) (Table1).

In overall, most of the patients with underlying diseases (73%) had EPTB and DTB. DTB was found in patients with BCGosis, defects of the IL-12/IFN-γ Axis, HIV, hepatitis C and CGD.

Distribution of PTB and EPTB in females was not statistically different (46% and 48%, respectively) (P >0.05) and were much higher than DTB (6%) (P <0.05). Distribution of DTB in males was higher than in females (36% vs. 6%) (P <0.05), but other forms of TB had lower distribution in males (33% for PTB and 31% for EPTB) (P >0.05).

In patients < 1 year, DTB was the most frequent type (48%), followed by PTB (28%) and EPTB (24%). However, in patients older than 1 year, both PTB and EPTB had similar distributions (42%) and they were more frequent than DTB (16%). There was significant difference between distribution rates of DTB in two age groups (P <0.05).

Clinical manifestations of the patients were listed in Table 2. Weight loss (83%) and long-term fever (80%) were the most common symptoms.

The acid fast staining of body secretions was positive in 32 cases (35.5%). A positive smear was more common in children ≥1 year and children with EPTB (31%) and PTB (28%). TST was performed for 89 patients and 83 cases (92%) had positive result. Urine cultures were positive in 5 cases (5.5%) and *Escherichia coli* (4 patients) and *Candida* spp. (1 patient) were isolated from them. In 5 patients (7%), blood cultures were positive and organisms such as *Pseudomonas aeruginosa*,

Table 1. Baseline characteristics of children with TB infection

Characteristic	N (%)
Age (year)	
<1	21 (23)
1-4	25 (28)
5-12	38 (42)
13-18	6 (7)
Gender	
Male	55 (61)
Female	35 (39)
Race	
Iranian	79 (88)
Afghan	11 (12)
TB History in family	20 (22)
Underlying disease	
HIV	6 (7)
CGD	7 (8)
BCGosis	10 (11)
Defects of the IL-12/IFN-γ Axis	5 (5.5)
LAD 1	2 (2)
SCID	2 (2)
CVID	1 (1)
Bernard Soulier syndrome	1 (1)
Down syndrome	1 (1)
Hepatitis C	1 (1)
Trisomy 9	1 (1)
Cystic fibrosis	1 (1)
Site of TB infection	
Pulmonary Tuberculosis	34 (38)
Extra Pulmonary Tuberculosis	35 (39)
Lymphadenopathy	6 (17)
Meningitis	2 (6)
Peritonitis	6 (17)
Skeletal TB	13 (37)
Endocarditis	1 (2)
TB of the CNS	3 (9)
Cutaneous TB	4 (11)
Disseminated TB	21 (23)
Outcome	
Discharge	80 (89)
Expire	9 (10)
ND	1 (1)

TB, Tuberculosis; HIV, Human Immunodeficiency Virus; *CGD*, Chronic Granulomatous Disease; LAD 1, Leukocyte adhesion deficiency-1; SCID, Severe Combined Immunodeficiency; CVID, Common variable immune deficiency; ND, No Data.

Table 2. Symptoms of children with TB infection

Complaint	N (%)
Weight loss	75 (83)
Prolonged fever	72 (80)
Chronic cough	49 (54)
Lymphadenopathy	40 (44)
Respiratory distress	37 (41)
Hepatomegaly	28 (31)
Splenomegaly	22 (24)
Ascites	12 (13)
Abscess	12 (13)
Peritonitis	11 (12)
Chronic diarrhea	10 (11)
Skin lesion	7 (8)
Clubbing	4 (4)
Meningitis	3 (3)
Endocarditis	1 (1)

Streptococcus viridians, *Klebsiella* spp. and *Salmonella* serogroup D were isolated. CSF culture was positive in only one patient and *Klebsiella* spp. was isolated. *Mycobacterium tuberculosis* was not isolated from urine, blood or CSF cultures of any patients, whereas it was isolated from gastric cultures of 11 patients (12%). HIV infection was confirmed by detection of HIV antibody in patients (6 cases). PCR test for detection of *M. tuberculosis* was performed for 74 patients and it was positive in 52 patients (70%). Specimens such as sputum, lymph node, bone marrow, Bronchoalveolar lavage (BAL), ascites, pleural fluid, gastric lavage, skin rash, lumbar and brain abscess, peritoneal fluid, CSF fluid, synovial fluid and intestinal biopsy were used for this assay (Table 3).

Table3. Microbiological diagnosis of TB infection

Test	N (%)
Acid fast staining	32 (35.5)
TST	83 (92)
Urine culture	5 (5.5)
Blood culture	5 (5.5)
CSF culture	1 (1)
HIV antibody	6 (7)
Gastric culture	11 (12)
TB PCR	52 (58)

TST, Tuberculin Skin Test; CSF, Cerebrospinal Fluid; HIV, Human Immunodeficiency Virus; TB, Tuberculosis; PCR, Polymerase Chain Reaction.

Chest radiography (CXR) was done in 80 patients (89%) and it was normal in 32 patients (35.5%) (Table 4).

Computed tomography (CT) scan was performed in 29 patients (Table 4) and 27 cases (30%) showed abnormal results including post mediastinal mass, lymphadenopathy, atrophy of cortex, lung cavity, hepatosplenomegaly, nodularity in spleen and lung, brain abscess, pleural effusion, hydrocephaly, bronchiectasis, osteomyelitis, collapse consolidation, peritonitis and pneumonia.

Sonography was used for 40 patients (45%) (Table 4) and its abnormal findings were as follows: hepatomegaly, calcification in spleen, hepatosplenomegaly, ascites, liver cysts, arthritis, hypoecoic lesions in liver and spleen, pleural effusion, calcificated granuloma in liver, and lymphadenopathy.

Biopsy was pathologic in 24 cases (27%) and showed granuloma in rectosigmoid, skin, peritoneal tissue, liver, mediastinal mass, and lymph nodes, Aspergillus in brain and lung abscess, nodule in transverse colon, acid fast bacilli in bone marrow, lymph nodes and lung, infiltration of histiocyte and giant cells in peritoneum, and granulomatous inflammation in duodenum.

Table 4. Radiological and histological tests

Test	N (%)
CXR	
Pathologic	48 (53.5)
Normal	32 (35.5)
ND	10 (11)
Sonography	
Pathologic	34 (38)
Normal	6 (7)
ND	50 (55)
Ct-scan	
Pathologic	27 (30)
Normal	2 (2)
ND	61 (68)
Biopsy	
Pathologic	24 (27)
ND	66 (73)
MRI	
Pathologic	4 (4)
ND	86 (96)
Endoscopy	
Pathologic	3 (3)
ND	87 (97)

CXR, Chest X-ray; ND, No Data; Ct-scan, Computed tomography scan; MRI, Magnetic resonance imaging

Hematologic studies (Table 5) showed that 24 patients (27%) had leukocytosis and level of their white blood cells (WBC) was elevated. Leukopenia was seen in 3 patients (3%) and their WBC count was lower than 4000 cell/μL. Neutrophiliawas observed in 1 patient (1%), while 39 cases (43%) had neutropenia. Fifty-two cases (59%) were diagnosed as having lymphocytosis and lymphocytopenia was detected in 9 patients (10%).

In overall, 80 patients (89%) discharged and 9 patients (10%) died. There was no information about the treatment outcomes of one patient. The treatment success rate in females was 94% that was higher than in males, which was 87%. All deaths occurred in the Iranian population. Among the dead patients, 8 patients were suffering from underlying diseases such as BCGosis, HIV, HIV and CF, HIV and Hepatitis C, LAD 1, SCID, defects of the IL-12/IFN-γ Axis and CVID.

Discussion

In this study, the analysis of medical records of 90 patients with TB demonstrated that the annual prevalence rates of TB in an Iranian referral hospital had fluctuations in different years, which can be due to the differences in the numbers of TB cases and the total number of patients admitted to the hospital in each year. According to the results, it can be stated that the prevalence of pediatric TB in our study had an increasing trend till 2010 and then decreased in recent years.

In our study, the most prevalent age for TB infection was 5-12 years and most of our patients were males (61%). Wu *et al.*, (10) from china reported similar sex and age distributions, but in other studies female patients were more than males and most of them were 15-18 years old (2,12). The discrepancy about the most common infected age group between our study and other investigations can be related to the age ranges that were evaluated in each study.

About 22% of children have been in contact with adults with active tuberculosis. In previous studies, positive source contact was identified in 44.5% and 56% of the TB infected children (2,10). Close contact with infected adult increases the transmission risk of infection to the children (10); therefore, contact investigation can be a useful tool for diagnosis of TB in children.

In the current study, the prevalence of PTB and EPTB were close together (38% vs. 39%) and was higher than DTB (23%). In agreement with this finding, a study in Nepal (13) reported close prevalence of PTB and EPTB (46.3% and 41.4%, respectively) that were higher than DTB (7.4%). In some studies, DTB was considered as a subset of EPTB, so their results were different from ours and EPTB was the most form of TB (3,14). It was also found that DTB was more frequent in children < 1 year that was in consistent with previous reports (2,10,15). This can be due to the weaker immune responses in infants and reduced recruitment of monocytes to the infection sites (16).

Thirty-three percent of investigated patients had underlying diseases. Results demonstrated that DTB was frequent among patients with BCGosis, defects of the IL-12/IFN-γ Axis, HIV, Hepatitis C and CGD. In agreement with this study, Sharifi Asadi *et al.*, (17) reported that definitive immunodeficiencies such as SCID, T-cell deficiency, CGD and HIV were observed among 39% of their patients with DTB. Studies revealed that genetic and acquired defects in immune responses raise the risk of disseminated and lethal mycobacterial disease (16,18,19).

HIV/TB co-infection was observed in 7% of patients, which was similar to the results reported by Moyo *et al.,* (6%) from South Africa (15) and was lower than the results of Jain *et al.,* (26.8%) form India (20), Tilahun *et al.,* (28.2 %) from Ethiopia (21) and Mandalakas *et al.,* (22%) from the USA (22). The differences in the rates of HIV co-infection in different studies may be related to the total number of studied patients and the overall incidence of HIV in each region.

Thirty-five percent of children were smear positive and it was more common in female children and in children older than 1 year. These findings were in agreement with the results of other studies (2,8,21,23). The reasons for low rate of smear positivity in the children can be due to the paucibacillary nature of infection in children and their inability in expectorate enough sputum for microscopy examination (24).

In this study, the rate of positive culture for *M. tuberculosis* was lower than positive smear (12% vs. 35.5%) that can be due to the low volume of specimen or presence of non-viable bacteria in the sample of pretreated patients that only were detected by microscopy (25).

The mortality rate in our study (10%) was similar to the mortality rate reported by Molaeipoor *et al.,* (11%) (14) But was higher than the rates reported by Alavi *et al.,* (2.2%) (8) and Tilahun *et al.,* (1.8%) (21). However, in some studies mortality rates were higher than our study (3,21,24). In this study, age, type of TB and underlying diseases were potential risk factors that led death in patients and increased the mortality rate.

Conclusions

This investigation demonstrated that the total prevalence rate of TB was 56.6 per 100,000 admitted patients in an Iranian referral hospital. The prevalence of PTB and EPTB in children was similar, while it was higher than DTB. DTB was more frequent in children under 1 year and in children with underlying diseases. Given the fact that the mortality rate is higher in infants, children with DTB and children with underlying diseases, early detection and treatment of these patients will help to reduce the mortality rate of TB disease.

Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Tehran University of Iran ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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