Pediatric tuberculosis in Turkey: a review of 8-years period in a tertiary care hospital

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Received: 10 April 2015, Revised: 13 July 2015, Accepted: 9 December 2015

SUMMARY: Bayhan Gİ, Tanır G, Metin Ö, Şimsek H, Aydın-Teke T, Öz FN, Gayretli-Aydın ZG. Pediatric tuberculosis in Turkey: a review of 8-years period in a tertiary care hospital. Turk J Pediatr 2015; 57: 431-438.

The purpose of this study was to evaluate the clinical, radiological, microbiological characteristics, side effects of anti-TB drugs and treatment outcome of childhood definite or probable TB. The medical records of all childhood TB patients were investigated in the department of pediatric infectious disease of a tertiary care hospital between January 2005 and December 2012. Patients who followed-up until the anti-TB treatment was completed were included in the study. One hundred forty four pediatric cases with active TB were included in the study (27 definite, 117 probable). Twenty-four (16.7 %) patients were asymptomatic at admission. Pulmonary TB was the most common type. The most common localizations for extrapulmonary TB were superficial lymphadenitis. An index case was detected in 39.6% of the patients. In conclusion, the absence of constitutional symptoms does not exclude TB. Household contact screening plays an important role in the diagnosis of childhood TB especially in asymptomatic patients.

Key words: childhood, Mycobacterium tuberculosis, lymhadenopathy, chest X-ray, computedtomography.

Tuberculosis is always an important public health issue and diagnosis of childhood tuberculosis is still difficult. The World Health Organization (WHO) estimates that there were 9 million people with TB disease worlwide and 1.5 million died from the disease. 550,000 children became ill with TB in 2013 [1]. According to a 2013 report of WHO, in Turkey, the annual TB incidence is 20/100,000 population and prevalence is 23/100,000 [2]. TB cases in children point to the ongoing transmission and these cases are commonly encountered in regions where the adult TB control measures are insufficient. Given the low bacillus load and inability to provide adequate sputum specimens, childhood TB cases have low definite diagnosis rates [3,4]. In this retrospective study, we aimed to describe clinical manifestations, epidemiologic features, diagnosis, treatment and outcomes of pediatric TB patients in a TB referral center in Turkey.

Material and Methods

Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Center is known as a reference center for pediatric TB cases; it is a member of the TB active surveillance program, which was started in 2005 with the cooperation of seven anti-TB combat health units in Ankara. In this retrospective descriptive study we aim to evaluate our pediatric TB patients since January 2005, the date on which active surveillance was begun. The medical records of patients who were diagnosed as TB, below 18 years of age and treated at least with a three-drug anti-TB

regimen were collected from hospital medical database between January 2005 and December 2012. Patients who continue to follow in another center after starting treatment were excluded. The patients with BCG lymphadenitis were not included in this study. The records of these patients were reviewed with respect to demographic and clinical characteristics, contact history with an adult index case, the results of tuberculin skin test (TST), microbiological, radiological and if available histopathologic findings.

The positive TST results corresponding to Bacillus Calmette–Guérin (BCG) vaccinated, non-vaccinated and immunosuppressive cases were defined as indurations of ≥ 15 mm, ≥ 10 mm and ≥ 5 mm, respectively. Positive BCG vaccination was confirmed by the presence of a scar on the left shoulder. If there is not BCG scar, the patients were accepted as non-vaccinated. All chest radiographs were evaluated by a radiologist. Acid-fast bacillus (AFB) staining, mycobacteria polymerase chain reaction (PCR) and mycobacterial culture were performed with various samples, including sputum, fasting gastric washings, pleural fluid, cerebrospinal fluid (CSF), synovial fluid, abdominal effusions, and lymphadenopathy (LAP) biopsies.

Irrespective of the disease location, all patients in the study were classified into two groups as definite or probable TB cases. The definite TB cases were defined as having at least one positive result in a clinical sample regarding AFS and/or culture and/or PCR tests. Detection of a caseating granuloma or AFS in a single histopathologic specimen was also considered to indicate a definite case. Probable TB cases had been defined by whether they met three or more of the following criteria: 1) nonspecific TB symptoms such as fever, cough, and weight loss, 2) chest X-ray or CT findings suggesting active TB, 3) presence of extrapulmonary active TB findings on other radiologic examinations, 4) contact history with an adult index case, 5) TST positivity, and 6) presence of good response to anti-TB therapy.

The patients were further classified as pulmonary or extrapulmonary TB. Pulmonary cases involved TB of lung parenchyma, pleura and intrathoracic lymph nodes, while extrapulmonary TB cases had involvement of extrapulmonary organs and tissues. The adults who were diagnosed as active pulmonary TB and reported to have a household contact history with the pediatric case were defined as an index case. In order to detect the index cases, all family members having contact with our cases and their intimate friends were directed to anti-TB combat units to provide screening.

Miliary and CNS TB patients received a minimum one year of therapy designed as four drugs (INH, rifampicin, pyrazinamide, and ethambutol) through the first two months, followed by two drugs (INH, rifampicin). The treatment durations and procedures were modified according to presence of contact with a multi-drug resistant adult TB patient, presence of underlying immunosuppression, or occurrence of drug side effects and unexpected treatment responses. An additional steroid treatment was implemented to definitely diagnose CNS and miliary TB cases. Patients who exhibited pleural and pericardial effusions due to TB also received steroid therapies.

The patients were called for monthly follow-up visits and monitored for drug side effects. Following the combination of treatments, follow-up visits were planned at a six- month interval for the first year and annually for subsequent years. Anteroposterior and lateral chest X-ray examinations were performed at each follow-up visit.

The Statistical Package for the Social Sciences (SPSS) 15.0 version was used for the statistical analysis. For categorical variables, chi-square test, and for continuous variables, Mann-Whitney U and t-tests were utilized. Value of significance was accepted as $P < 0.05$.

Results

A screening of the hospital information system revealed a total of 144 active TB cases.

Of the 144 patients who were included in the study, 80 (55.6 %) were male and 64 (44.4 %) were female. Nineteen (13.2 %) patients were aged less than 1 year, 47 (32.6 %) were 1-4 years, 43 (29.9 %) were 5-9 years, and 35 (24.3 %) were ≥ 10 years. An index case was detected in 57 (39.6 %) patients. Two (1.4 %) patients had contact history with more than one adult active TB patient.

Table I. Symptoms and Signs of the Patients with Definite and Probable TB.

Symptoms/signs	Definite TB n (%)	Probable TB n (%)	P	Total n (%)
Asymptomatic	1 (3.7)	23 (19.7)	0.047	24 (16.7)
cough (≥ 2 weeks of duration)	11 (40.7)	69 (59)	0.08	80 (55.6)
Fever	5 (18.5)	26 (22.2)	0.67	31 (21.5)
Night sweating	8 (29.6)	26 (22.2)	0.41	34 (23.6)
Weight loss	6 (22.2)	16 (13.7)	0.26	22 (15.3)
Anorexia	5 (18.5)	18 (15.4)	0.68	23 (16)
Expectorate of sputum	5 (18.5)	19 (16.2)	0.77	24 (16.7)
Listlessness	1 (3.7)	11 (9.5)	0.46	12 (8.3)
Erythema nodosum	1 (3.7)	0 (0)		1 (0.7)
Hemoptysis	0 (0)	3 (2.6)		3 (2)
Abdominal pain	0 (0)	5 (4.3)		5 (3.5)
Ascites	1 (3.7)	1(0.9)		2 (1.4)
Enuresis - diurnal	1 (3.7)	0 (0)		1 (0.7)
Visual impairment	0 (0)	1 (0.9)		1 (0.7)
Hematuria	0 (0)	1 (0.9)		1 (0.7)

One hundred twenty patients presented with symptoms suspicious of TB whereas totally 24 (16.7%) patients were asymptomatic at admission. Twenty-one of these 24 patients had been detected during a screening for their close contact with a TB case. Nevertheless, TB diagnosis of two patients had been made during the investigation prior to their steroid therapy for a rheumatologic disease. One patient was diagnosed after the detection of a positive TST during the school screening.

Overall, case definitions were definite TB in 27 (18.7%) and probable TB in 117 (81.3 %). Symptom frequencies and comparison of definite and probable cases are shown in Table I. The most frequent symptom was coughing (≥ 2 weeks of duration) in both groups. Comparison of symptoms between the two groups revealed significance only for being asymptomatic in probable TB group (P = 0.455). Comparison of definite cases and probable cases revealed a significant difference only for having pulmonary or extrapulmonary TB (P = 0.000). Higher pulmonary TB rates were seen in probable cases than definite cases. Table II demonstrates the comparison of demographical, epidemiological, microbiological, radiological, histopathological characteristics, presence of BCG scar, TST positivity and being pulmonary or extra-pulmonary disease of the patients with probable or definite TB.

Pulmonary TB was the most common type in both groups. The most common localizations for extrapulmonary TB were superficial lymphadenitis, central nervous system (CNS) and abdominal TB. Table III shows the TB localization and frequencies with respect to definite/probable case groups. Contact with an index case was detected in 54 (44.3%) of the patients with pulmonary TB and 3 (13.6%) of the extrapulmonary. Identification of index case was more in patients with pulmonary TB than extrapulmonary TB (P = 0.008).

BCG scar information was obtained in 125 patients. One hundred and seven (85.6%) of them were detected to have a BCG scar. TST was performed in 135 patients, and was positive in 96 (71.1%) children. A microbiologic confirmation was provided in 27 (18.7%) patients. AFB, PCR and culture of *Mycobacterium tuberculosis* results were summarized in Table II. AFB, PCR or culture tests were not available in 42 (29.1%) patients. In 22 (15.3%) patients, histopathologic examination was performed, and 15 (68.1%) of them exhibited findings supporting TB. The most common histopathologic finding was caseating granuloma (n: 10), and the others were caseating granuloma with AFB positivity (n: 3) and AFB positivity without any histopathologic clues (n: 2). The patients with caseating granuloma without AFB positivity

Table II. Demographical, Epidemiological, Microbiological, Radiological, Histopathological Characteristics, Presence of BCG Scar, TST Positivity and Being Pulmonary or Extra-Pulmonary Disease of the Patients with Probable or Definite TB

Clinical characteristics at admission	Definite TB n = 27 (%)	Probable TB n = 117 (%)	P	Total n (%)
Mean age (month) ± SD	74.8 ± 62.8	78.2 ± 52.7	0.794	76.3± 54.8
Gender female/male ratio	0.93	0.77	0.667	0.8
Presence of BCG scar (of 125 patients with available BCG scar information)	21 (84)	86 (86)	0.757	107 (74)
Contact with active TB	9 (33.3)	48 (41)	0.51	57 (40)
TST positivity	17 (73.9) (of 23 patients)	79 (70.5) (of 112 patients)	0.74	96 (66.7)
Pulmonary TB	15 (55.6 %)	107 (91.5 %)	0.000	122 (84.7)
Extra-pulmonary TB	12 (44.4 %)	10 (8.5 %)		22 (15.3)
Radiologic findings consistent with TB	26 (96.3 %)	114 (97.4 %)	0.56	140 (97.2)
AFB positivity	13 (of 20 patients)	0 (of 76 patients)	0.000	13 (9)
Culture positivity	8 (of 15 patients)	0 (of 45 patients)	0.000	8 (5.6)
PCR positivity	8 (of 16 patients)	0 (of 52 patients)	0.000	8 (5.6)
Pathologic findings consistent with TB	15 (of 15 patients)	0 (of 7 patients)	0.000	15 (10.4)

TB: tuberculosis, BCG: Bacillus Calmette-Guerin, PCR: polymerase chain reaction, TST: tuberculin skin test, AFB: acid-fast bacillus.

were examined in terms of other agents which can cause caseating granuloma (*Bartonelle henselae, Francicella tularensis* etc.) and other etiologic agents were excluded.

The chest X-ray and CT findings of all pulmonary TB patients are summarized in Tables IV and V. Chest CT examination was performed in 116 (80.5%) patients. Thirty (24.6%) patients who lacked X-ray results supporting TB were diagnosed based on the chest CT findings.

Treatment protocols as three-drug (isoniazid, rifampicin, pyrazinamide), triple (isoniazid, rifampicin, ethambutol) or four-drug (isoniazid, rifampicin, pyrazinamide, ethambutol) were prescribed to 127 (88.2%), 6 (4.2%) and 4 (2.8%) patients, respectively. The treatment of TB meningitis and miliary TB was managed with isoniazid, rifampicin, pyrazinamide, and ethambutol. Drug resistance was not detected in positive myobacterial cultures. Side effects of anti-TB drugs occurred in 14 patients (9.7%), but only two of them required treatment modifications. Due to a 3 to 5 fold increase in liver enzymes in six patients, anti-TB treatment was stopped and later restarted after normalized of liver enzymes. Isoniazid-induced urticarial vasculitis was seen in one patient with CNS and pulmonary TB and managed by changing the regime to rifampicin, morphazinamide, ethambutol, and streptomycin. In a patient receiving isoniazid, rifampicin and pyrazinamide, major toxic hepatitis was developed and subsequently treated with isoniazid, rifampicin and ethambutol. Pyrazinamide-induced hyperuricemia developed in six patients and 9-month-treatment with isoniazid and rifampicin was commenced.

Treatment success, defined as cured when treatment completed, was achieved in all of the patients. Treatment compliance problem did not occur in any patient. There were not any relapse cases.

Table III. Site of TB with the Respect to Definite/Probable TB Patients

Site of TB	Definite TB n (%)	Probable TB n (%)	Total n (%)
Pulmonary	14 (51.9)	103 (88)	122 (84.7)
Pulmonary + abdominal	1 (3.7)	1 (0.9)	
Pulmonary + pericardial	0 (0)	2 (1.7)	
Pulmonary + CNS	0 (0)	1 (0.9)	
Lymph node	8 (29.6)	2 (1.7)	10 (6.9)
CNS	0 (0)	3 (2.6)	4 (2.7)
CNS + Pott' s disease	1 (3.7)	0 (0)	
Abdominal	1 (3.7)	4 (3.4)	5 (3.5)
Bone and joint (osteomyelitis)	1 (3.7)	0 (0)	1 (0.7)
Ocular	0 (0)	1 (0.9)	1 (0.7)
Disseminated	1 (3.7)	0 (0)	1 (0.7)

TB: tuberculosis CNS: central nervous system

Table IV. Chest X-ray Findings of Pulmonary TB Patients

Signs	N	% (of the 122 patients)
Consolidation	76	62.2
Peribronchovascular thickening	26	21.3
Hilar lymphadenopathies	17	13.9
Atelectasis	9	7.3
Pleural fluid	3	2.5
Cavitation	1	0.8
Hyperinflation	3	2.5
Ghon complex	1	0.8
Normal	30	24.6

TB: tuberculosis, CNS: central nervous system

Discussion

The 2011 National TB Combat Report of Turkey notified that 4.9% of the total 15.679 TB patients were in the 0-14 age group and 23 % in the 15-24 age groups[2]. Adults are the main sources of pediatric TB cases, and pediatric TB patients reflect the ongoing transmission within the population [5]. In a study from California, authors found that the number of patients in the 0-4 age group was 2-4 times higher than the number in the 5-14 age groups [6]. Similar to our study in a multicenter study from Turkey, the mean age of pediatric TB patients was found as 7 years, and there was no significant differences found in frequency among age groups [7]. Moreover, there was a homogeneous distribution among age groups in our study, although <1 year group was smaller than the other age groups.

The symptoms of TB in pediatric cases are nonspecific, and their clinical and diagnostic significances have been the subject of many studies. Persistent cough, new-onset fatigue and fever are reported to have high sensitivity and specificity. Systemic complaints such as fever, night sweats, anorexia and decreased activity occur less often[8-12]. In the pediatric TB case series the rate of asymptomatic patients reported as 11 to 23.4% [9,10]. We detected active TB in 24 asymptomatic children. In addition, symptoms other than cough were detected in less than one-third of our patients. We thus consider that absence of symptoms is not reliable to exclude the pediatric TB diagnosis. Most of asymptomatic cases in our study had been diagnosed during a screening of adult TB contacts. Distinction of latent and asymptomatic patients with active TB is a major concern in that asymptomatic patients

Table V. Chest CT Findings of Pulmonary TB Patients

Findings	N	% (of 116 patients)
Consolidation	38	32.7
Mediastinal lymphadenopathies	50	43.1
Hilar lymphadenopathies	34	29.3
Fibrotic band	25	21.5
Ground glass opacities	20	17.2
Atelectasis	25	21.5
Nodule	14	12
Interstitial thickening	11	9.4
Pleural fluid	6	5
Branching tree view	5	4.3
Cavitation	3	2.5
Ghon complex	3	2.5
Mass	3	2.5
Pleural thickening	2	1.7
Round pneumonia	1	0.8

TB: tuberculosis

are frequently misdiagnosed as latent TB and receive prophylactic drugs, which results in drug resistance.

Family screening is very important to identify the index case and other secondary TB cases. Detection of undiagnosed cases is an important measure in preventing TB spread. Many studies suggest contact screening to be very beneficial for new case detection. In a study from Taiwan, by screening 4595 household contacts, 284 (6.2%) new active TB patients had been diagnosed [13]. In another study, totally 6613 children had been screened due to contact with adult TB patients, and 121 new active TB cases were found [14]. If pediatric TB case is the firstly defined TB in the family, other secondary sources are more easily accessed [7]. We found a history of TB contact in one-third of our pediatric cases. The most common index cases were family members and first-degree relatives. We considered that contact history with an adult TB case to be a very important clue for TB diagnosis. A strong linkage between TB contact and pulmonary TB, while patients without contact history exhibited more extrapulmonary disease was reported. Authors concluded that lack of contact history may lead to delayed diagnosis and spread of the disease to extrapulmonary organs [14,15]. Similarly, in our study TB contact history was higher in patients with pulmonary TB than patients with extrapulmonary TB.

Extrapulmonary TB is more common in children than adults. Extrapulmonary TB rate was reported between 12-25.8% according to studies that included various age groups and from various countries and settings. The most common site of extrapulmonary TB is different among the studies also, some reported it as superficial lymphadenitis others as CNS or miliary [7,11,15-18]. In the present study most common sites of extrapulmonary TB were superficial lymphadenitis. CNS disease, especially TB meningitis, is the most serious complication of TB in children [6,9,16]. It has been reported that around 10% of cases with TB meningitis have some form of spinal tuberculosis. Pott's disease accounts for the majority of all cases. In this study, our patient with Pott's disease had TB meningitis as well. It is kept in mind that Pott's disease may be associated with meningitis. It was reported that the diagnostic yield for extrapulmonary TB was low even when invasive methods were used for sample collection. Among the extrapulmonry TB cases, confirmation ratio was reported as 9.1% [19]. In contrast to literature, in our study among the EPTB cases had higher definition rate. Twelve of 22 cases had definite TB whereas 10 of them had probable TB.

Collection of airway samples is limited in children and this leads to obstacles in determination of *Mycobacterium tuberculosis*. It has been reported that in pediatric TB cases, AFB positivity was 18-25 %, PCR detection was 19.7-66.3 %, and culture positivity was 14.8-58 %. It has been suggested that mean age

was lower in probable TB cases than definite cases, furthermore higher AFB and culture positivity were most likely in patients over 10 years old [7,15,19]. The authors stated that these results may be linked to limitations in proper sample collecting in younger children and higher bacillus loads in older patients [20]. Although AFB, culture and PCR positivity were low in our study, because of retrospective nature of our study, microbiological tests results are not available in all of the patients. The number of patients with definite TB confirmed by microbiological tests was much lower than that of probable TB. Since the microbiologic diagnosis of pediatric TB has many limitations, additional tools should be considered in the pediatric age group. The combination of compatible clinical symptoms, radiologic findings, contact with active adult TB patient, and good treatment response to anti-TB medications should be evaluated carefully. Such an approach contributes particularly to the diagnosis of probable cases. It has been reported that pediatric pulmonary TB cases may exhibit lower AFB and culture positivity rates than extrapulmonary TB infections [8,10]. In our study, group relative frequency of definite cases was higher in patients with extrapulmonary TB.

Chest X-ray is widely used for the detection of pulmonary TB. The most frequently encountered chest X-ray findings for pediatric TB cases are consolidation, hilar-mediastinal LAP and pleural effusion, whereas the rarer findings include paratracheal LAP, miliary images, primary complex and normal-appearing chest X-ray [16,20,21]. The sensitivity and specificity of chest X-ray in children are low. In one study, 70% specificity and 40% sensitivity for chest X-ray had been reported; despite the presence of LAP on CT, chest X-ray was normal in more than half of the patients [22]. Chest CT imaging has been reported as useful in demonstrating early pulmonary disease, such as cavitation, and intrathoracic hilar lymphadenopathy [12]. In one study, chest CT images of pulmonary TB were compared against community-acquired pneumonia in a group of children. Ultimately focal-subsegmental opacities and hilar-mediastinal LAPs were found to be higher in TB cases; necrotic and calcified lymph nodes may strongly associate with TB [22]. The most common chest X-ray findings in our study were infiltration, peribronchovascular thickening and hilar LAP. The most common chest CT findings were consolidation and mediastinal-hilar LAP. Furthermore, in contrast to normal images of chest X-ray in one-quarter of our patients, chest CT examination revealed diagnostic findings. Therefore, we suggested that chest CT could be useful in patients with positive TST, having contact with an index case, in the presence of strong clinical suspicion, irrespective of a normal chest X-ray. CNS disease, such as TB meningitis or tuberculoma, may also be identified on CT imaging, especially as contrast demonstrates meningeal enhancement. Magnetic resonance imaging has been found to be useful for musculoskeletal TB, particularly involving bones and joints [12].

A three-drug regimen has been shown to have success rates of greater than 95% and low adverse reaction rates [12]. Our patients with pulmonary TB, and extrapulmonary TB except disseminated TB, TB meningitis, Pott' s and TB osteomyelitis were successfully treated with six month - three-drug regimen. Four-drug regimen had been used for the treatment of patients with disseminated TB, TB meningitis, Pott's disease and TB osteomyelitis. Standard anti-TB drug regimens are remarkably well tolerated among pediatric patients, and rarely lead to severe life- threatening side effects, possibly necessitating omission of some major agents [9,23]. According to a study from our country, among 2205 pediatric TB cases, no side effects of anti-TB drugs were observed; only a temporary rise in liver enzymes involving 67 patients was reported [17]. In a study of 1-5-year-old TB cases, reported side effects were as follows; allergic cutaneous reaction linked to rifampicin, rise in liver enzyme linked to pyrazinamide and impaired sight linked to ethambutol 15 mg/kg in three patients [24]. In our study hepatotoxicity was found as the most common side effect. As severe side effects, urticarial vasculitis and major hepatitis were seen in two patients. We did not encounter any visual side effect with 20 mg/kg ethambutol treatment, which is reported to be safe by WHO. It has been reported that compliance is a major determinant of the success of drug treatment – compliance of the physician in prescribing the optimum appropriate regimen and monitoring it, and compliance of the patient in taking the medication as prescribed [12]. In our study patients were followed for monthly

visits and monitored for drug side effects. Our study indicates that anti-TB treatment is safe in pediatric patients. The treatment success in our study may be linked to the fact that compliance of the patients to the treatment, regular follow-up of the patients and absence of HIV-positive or severe malnutrition cases, drug resistance in addition to fewer CNS TB patients.

Our study was limited by a single center hospital based study design. However, our hospital is a pediatric TB referral hospital with the cooperation of seven anti-TB combat health units in Ankara, capital city of Turkey located in the Central Anatolia Region. Owing to this referral hospital setting, our study sample may be representative of pediatric TB experiences at Central Anatolia Region.

In conclusion, the absence of constitutional symptoms does not exclude TB in children. Asymptomatic pediatric TB patients could be detected during a screening of adult TB contacts. For this reason screening of TB contacts is crucial in pediatric TB diagnosis. The number of patients with definite TB confirmed by microbiological tests may be low in childhood TB. Regular follow-up to compliance of the patients to the treatment and monitorization of drug side effects and response to anti-TB therapy are important issues in the management of pediatric TB.

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