

Demographic and microbial characteristics and drug resistance of childhood tuberculosis in Istanbul: analysis of 1,541 cases

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Abstract

Introduction: Although tuberculosis (TB) is frequently seen in Turkey, there are limited studies on childhood TB. We aimed to describe clinical and laboratory findings, including drug resistance, of children with TB in Istanbul, Turkey.

Methodology: The study included all children aged 0-14 years who were registered in public dispensaries between 2006 and 2010.

Results: The study included 1,541 cases. Forty-four percent (n = 763) of the patients were male with a mean age of 8.86±4.19 years. Fifty-five percent of the patients had pulmonary TB, 39% had extrapulmonary TB, and 6% had both pulmonary and extrapulmonary TB. The most common extrapulmonary involvement sites were the pleura (n = 193), lymph nodes (n = 247), and central nervous system (n = 41). Forty-one percent of the patients were evaluated microbiologically and 35% of them were positive. For the total study group, 14% of them were positive. A drug susceptibility test was performed on 108 patients. Drug resistance to at least one drug was detected in 16% (n = 17), to isoniazid in 15% (n = 16), streptomycin in 12% (n = 12), rifampicin in 9% (n = 10), ethambutol in 7% (n = 8), and multi-drug resistance in 8% (n=9) of patients.

Conclusions: This is the largest analysis on demographic features and drug resistance of childhood TB in Turkey. In Turkey, the rate of microbiological diagnosis is low, similar to rates worldwide. More microbiological studies and drug resistance tests should be done and annual changes should be followed with multi-center studies.

Key words: tuberculosis; child; pediatric; drug resistance; Turkey

J Infect Dev Ctries 2014; 8(3):304-309. doi:10.3855/jidc.3950

(Received 08 July 2013 – Accepted 19 September 2013)

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Introduction

Despite the availability of highly effective treatment for decades, tuberculosis (TB) remains a major global health problem. In 2011, there were an estimated 8.7 million new cases of TB, and 1.4 million people died from TB [1]. Recently, there has been renewed interest in childhood TB; it has been acknowledged to constitute a substantial burden of the global TB caseload [1]. Moreover, it is increasingly appreciated that the epidemiology of childhood TB reflects the success or failure of TB control programs, as pediatric TB is usually acquired from contact with an infectious adult [1-4].

TB remains a major public health problem in Turkey. The incidence of TB per 100,000 people was recently reported to be 28 by the World Health Organization (WHO) [1]. According to Turkish Health

Ministry data, the total number of registered cases of TB by 2009 was 17,400, and 958 (5.5%) of the cases were children between 0-14 years of age [5]. Although TB is a common disease in our country, there are limited studies – generally one-center studies – about the demographic characteristics of childhood TB [6-8]. In a global report by the WHO in 2011, it was declared that estimates of the numbers of TB cases and data among women and children should be better analyzed and reported [1].

In recent years, drug resistance has been on the rise throughout the world. There are few studies about drug resistance in childhood TB, and only one such study has been published in Turkey [9-11]. In this study, we aimed to evaluate the demographic characteristics and drug resistance of all childhood TB cases in Istanbul.

Methodology

In Turkey, the registration and follow-up of all patients diagnosed with TB is done in public dispensaries. The city of Istanbul, where the present study was performed, is the most crowded city of Turkey with a population of approximately 13 million. Because of continual migration from the rural areas of the country to Istanbul and the crowded conditions in which the migrated population lives, Istanbul has the highest TB incidence of Turkey. There are 33 public dispensaries in Istanbul. This study included all children aged 0-14 years of age who were registered in these dispensaries between 2006 and 2010. Demographic, clinical, and laboratory data of the patients were reviewed from the dispensary files.

Sputum and other samples from patients registered in these dispensaries were sent to the Central Microbiology Laboratory of the Istanbul Union Against TB. The Central Laboratory carries out the initial and follow-up microscopic evaluations of all registered patients. All samples were examined using concentrated smear microscopy. The samples were decontaminated and liquefied using a 4% solution of NaOH, and then concentrated by centrifugation for 15 minutes at 3.000 g. They were then examined using the Ziehl-Neelsen acid-fast stain method. Each sample was inoculated onto Löwenstein-Jensen slants as the stand-alone medium, and then incubated at 37°C for eight weeks. Culture-positive specimens were tested for susceptibility to isoniazid (INH), rifampicin (RMP), streptomycin (SM), and ethambutol (EMB). Susceptibility testing was performed using the indirect proportion method on Löwenstein-Jensen medium. The following drug concentrations were used to distinguish resistant isolates from susceptible isolates: INH, 0.2 µg/mL; SM, 10 µg/mL; RMP, 40 µg/mL; EMB, 2 µg/mL. Drug resistance was defined as growth on a drug-containing medium that is greater than 1% of that on the control medium. Single-drug resistance was defined as the presence of resistance to a single drug tested, and multi-drug resistance (MDR) was defined as resistance to at least isoniazid and rifampicin. Anti-TB treatment was given according to WHO criteria to all patients included in the study [12].

Statistical evaluations

During the assessment of the study data, the numerical parameters were described with mean, median, and standard deviation values, and the distributions of the categorical measurements by frequency and percentages were investigated. The SPSS for Windows version 13.0 (SPSS Inc.,

Chicago,USA) program was used for the statistical analysis.

Ethical approval was obtained from Bezmialem Vakif University Local Research Ethics Committee.

Results

The study included 1,541 patients with TB. Seven hundred and sixty-three (49%) of the patients were male with a mean age of 8.86±4.19 years (median, 10 years). Twelve of the patients were foreign nationals; the others were Turkish citizens. Of all patients, 1,510 (98%) were new cases. The demographic characteristics of the patients are presented in Table 1. The distribution of the frequencies of the 1,541 cases in each year were 342 (22.1%) in 2006, 329 (21.3%) in 2007, 308 (19.9%) in 2008, 292 (18.9%) in 2009, and 270 (17.5%) in 2010. The rates of childhood TB among the total TB cases in Istanbul per year were 5.72% (342/5,977) in 2006, 5.71% (329/5,754) in 2007, 5.48% (308/5,614) in 2008, 5.61% (291/5,200) in 2009, and 5.73% (270/4,712) in 2010. The rates of childhood TB did not change in each year.

Fifty-five percent of the cases had pulmonary TB, whereas 39% had extrapulmonary TB. The most common extrapulmonary involvement sites were the pleura, lymph nodes, and central nervous system (Table 1).

Microbiological evaluation (direct microscopy and/or culture) was done in 642 (41%) patients; 225/642 (35%) were positive. In the study population, 14% (225/1,541) of the patients were microbiologically positive. The microbial data of the patients are presented in Table 2. The drug resistance study was performed in 108 cases: 23 cases in 2006, 22 cases in 2007, 24 cases in 2008, 20 cases in 2009, and 19 cases in 2010. INH was the drug with the highest rate of resistance (15%) (Table 3). Resistance to at least one drug was seen in 17 cases (16%); the distribution of these cases among years was four (17.3%) in 2006, three (13.6%) in 2007, four (16.6%) in 2008, three (15%) in 2009, and three (15.7%) in 2010. There were eight boys (47%) in the 17 patients with resistance to at least one drug, and their mean age was 8.78 ± 3.12 years. Ten (58%) had pulmonary, and the rest extrapulmonary TB. Sixteen cases were new and a single case was a relapse. There was no statistical difference between TB groups with and without drug resistance related to age, gender, and type of TB.

Table 1. Demographic characteristics of the patients

		n	%
Gender	Female	778	49
	Male	763	51
Age	0-4 years	288	18
	5-9 years	478	32
	10-14 years	775	50
Definition of the cases	New case	1,510	98
	Relapse	31	1
	Treatment failure	0	0
Clinical manifestations	Pulmonary TB	848	55
	Extrapulmonary TB	607	39
	Pulmonary and extrapulmonary TB	86	6
Distribution of the extrapulmonary TB	Pleura	193	12
	Extra-thoracic lymphadenopathy	161	10
	Intra-thoracic lymphadenopathy	86	6
	Central nervous system	41	3
	Gastrointestinal system	34	2
	Miliary TB	27	2
	Genitourinary system	24	2
	Eye	17	1
	Musculoskeleton system	15	1
	Pericard	5	
	Skin	2	
	Salivary gland	2	

TB: tuberculosis

Table 2. Microbiologic data of the patients

		n	%
Direct microscopic examination	Positive	169	31
	Negative	372	69
	Total	541	
Culture	Positive	137	40
	Negative	207	60
	Total	344	
Total	Positive	225*	35
	Negative	417	65
	Total	642	

*In 72 of patients, both microscopical and culture positivity were found

Table 3. Results of drug sensitivity*

Drug	Sensitive		Resistant	
	n	%	n	%
Isoniazid	92	85	16	15
Rifampicin	98	91	10	9
Ethambutol	100	93	8	7
Streptomycin	96	88	12	12
At least one drug resistance	91	84	17	16
Isoniazid + rifampicin	99	92	9	8

*Drug sensitivity test was performed on 108 patients

Multi-drug resistance was observed in nine (8%) cases (2,2,1,2, and 2 cases in subsequent years, respectively). There was no treatment failure.

Discussion

In the current study, the data of all childhood TB cases in Istanbul between 2006 and 2010 were presented. It was established that the rates of childhood TB did not change between 2006 and 2010. The gender ratio was equal, and more than half of the cases were pulmonary TB. The most frequent extrapulmonary TB was TB lymphadenitis. Bacillus was detected in 35% of the patients through microbiological analysis. Drug resistance tests were done in only few patients, and the frequency of drug resistance did not change between 2006 and 2010. There was also no statistical difference between TB groups with and without drug resistance related to age, gender, and type of TB.

The incidence of TB has decreased during recent years in Turkey from 28.1/100,000 in 2006 to 24/100,000 in 2010 [5]. Similarly, the incidence has decreased from 56.7/100,000 to 44.1/100,000 in Istanbul. The rate of childhood TB among all cases is approximately 4.5% and did not change during the study period in Turkey [5]. Our study also showed that the rate of childhood TB in Istanbul has not changed over the years. As the trend of TB prevalence in Turkey and Istanbul decreased, the prevalence of childhood TB has also decreased.

In terms of the distribution of childhood TB in Turkey, 51% of cases are pulmonary TB, 43% are extrapulmonary TB, and 4% are both pulmonary and extrapulmonary TB, according to a recent report [5]. We found similar results; 55% of cases were pulmonary, 39% were extra pulmonary, and 6% were both intra and extrapulmonary. Similar results were found in terms of extrapulmonary involvement distribution; the pleura and extra and intra-thoracic lymph-nodes were the most prevalent sites [5]. Throughout the world, pulmonary parenchymal disease and intra-thoracic adenopathy are the most common clinical manifestations of pediatric TB, accounting for 60%–80% of all cases [13]. Among extrapulmonary manifestations, lymphadenopathy is the most common (67%), followed by involvement of the central nervous system, (13%) pleural TB (6%), miliary and/or disseminated TB (5%), and skeletal (4%) TB [14]. Compared with the rest of the world, the involvement sites were very similar in our study.

Definitive microbiological diagnosis and determination of antimicrobial susceptibility are

important in children. The major advantages of obtaining microbiological confirmation are the ability to make a definitive diagnosis and to perform drug susceptibility tests to exclude drug-resistant TB. In the era of increasing MDR and extensively drug-resistant TB, this information becomes critical to guide appropriate therapy [4]. Microbiological confirmation of TB is still rarely attempted in children, especially in primary care settings. However, even when samples can be obtained, since the disease is typically paucibacillary, the yield of direct acid-fast smear microscopy is very low, and prolonged mycobacterial culture is required. A major challenge of childhood TB is establishing an accurate diagnosis. Less than 15% of cases are sputum acid-fast bacilli smear-positive, and mycobacterial culture yields are 30%–40% [15-17]. Regional data from the WHO in 2007 showed that smear-positive TB in children under 14 years of age accounted for 0.6%–3.6% of reported cases [18].

In the Turkish Ministry of Health's data, only the microbiological results of pulmonary cases were reported for children; there were no data for total TB cases [5]. In our study, microbiological evaluation was done in 41% of patients, and 35% of them were proven microbiologically. The rate of microbiological identification was only 14% for the whole study population. The results of our study confirm the limitations of microbiological studies in childhood TB in Turkey and worldwide.

Apart from the limitations of the microbiological diagnosis of childhood TB, studies about drug resistance are also very rare. Neither microbiological evaluations nor drug susceptibility tests can be performed for all culture-positive patients. The WHO estimated that in 2008, 440,000 (3.6%) of the 9.4 million TB cases worldwide had MDR-TB. Comprehensive studies on resistance to anti-TB drugs in children are very few, because they are not included in global surveys [9,18,19]. Surveillance of anti-TB drug resistance between 1995 and 2007 among children from South Africa showed a significant increase in resistance to INH and RMP, from 6.9% to 15.1%, and an increase in MDR from 2.3% to 6.7% [18].

Correspondingly, there are no definite surveys about drug resistance in childhood TB in our country. Results of drug resistance for TB are generally from adult patients in Turkey; unfortunately, studies focused on children are very rare [11]. According to a recent report in Turkey, drug resistance was almost the same in a five-year period for all ages and throughout the country [5].

Table 4. Comparison of our drug resistance results with other studies performed in Turkey

Drug	Drug resistance (%)		
	Dilber <i>et al.</i> ^{11*}	Kilicaslan <i>et al.</i> ^{20**}	Our study
Isoniazid	6.7	12.5	15
Rifampicin	6.5	10	9
Ethambutol	4.2	4.4	7
Streptomycin	18.3	18	12
Overall drug resistance	26.7	24.8	16
Multidrug resistance	3.3	10.7	8

*Single-center study performed in childhood in Ankara, published in 2000; **Multi-center study performed in adults in Istanbul, published in 2002

Between 2005 and 2009 in Turkey, INH resistance changed from 11.5% to 13.1%, RMP changed from 6.7% to 6.5%, EMB changed from 4% to 4.7%, and SM changed from 8.1% to 8.5%, for all age groups, including adults. MDR, which was at 5.1%, did not change. A total of 19.1% of cases had resistance to at least one drug; total drug susceptibility was found to be 80.9% [5]. It is expected that rates of drug susceptibility in childhood are the reflection of adult rates. In our study, a drug susceptibility test was performed on 108 patients. The rate of drug resistance has not changed over the years and there was no statistical difference in terms of age, gender, and location of the disease during the study period. Rates of drug susceptibility for all of the drugs in this study were found to be higher when compared with Turkey's rates. As the rates in Istanbul were expected to be different from the rates in Turkey overall, the studies that were done in Istanbul were investigated. In a multi-center study from Istanbul involving 1,370 adult patients, the rate of resistance to at least one drug was found to be 24.8%, whereas the rate of resistance to INH was 12.5%, to RMP was 10%, to EMB was 4.4%, and to MDR was 6.7%; these rates were close to our results [20]. It can be concluded that anti-TB drug resistance rates are high in Istanbul. The only childhood drug resistance study from Turkey, published by Gocmen *et al.*, suggested that total drug resistance was 26.7%, followed by SM at 18.3%, INH at 6.7%, RMP at 6.5%, EMB at 4.2%, and finally, MDR at 3.3% in 60 TB cases [11]. When compared with our study, there was a decrease in total drug and SM resistances and a significant increase in INH, RMP, EMB, and MDR resistance (Table 4). Since Gocmen *et al.*'s study was a single-center study, it is hard to discuss the annual changes in the rates. Therefore, multi-center studies repeated every year should be done in order to compare the annual changes of drug resistance in childhood TB in Turkey.

Treatment success rate is 94% in Turkey [5]. We did not detect any cases with treatment failure.

The main limitations of the study include inaccessibility to the results of the tuberculin skin test, history of source case, rates of directly observed therapy in treatment, and other clinical and radiologic findings in children's medical charts.

Conclusion

Our study reflects the data about Turkey in general in terms of demographic characteristics and distribution of TB. In Turkey, the rate of microbiological diagnosis is low, which is similar worldwide. As there is limited data about childhood TB in terms of microbiology and drug resistance, more studies concerning these issues should be undertaken. Since TB is still one of the public health problems in Turkey, more multi-center studies are needed for the detection and follow-up of potential differences in childhood TB.

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Conflict of interests: No conflict of interests is declared.