Primary Antituberculosis Drug Resistance at Turkish Military Chest Diseases Hospital in Istanbul

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Key Words

Tuberculosis · Primary drug resistance · Turkey

Abstract

Objective: The aim of this study was to investigate the prevalence of primary drug resistance to tuberculosis.

Methods: We evaluated the clinical data, radiological features and sputum samples from 365 newly diagnosed patients with a positive culture of pulmonary tuberculosis at the Turkish Military Chest Diseases Hospital, Istanbul, Turkey. No patients had taken antituberculosis drugs previously. The Bactec method was used to perform drug susceptibility testing for isoniazid, rifampicin, ethambutol, and streptomycin. **Results:** Primary resistance to one or more drugs was detected in 87 (23.8%) patients; resistance to isoniazid was most common (54 patients) followed by resistance to ethambutol ($n = 39$), rifampicin ($n = 11$), and streptomycin ($n = 9$). One-drug resistance was detected in 69 patients; two-drug resistance in 11, three-drug resistance in 6, and four-drug resistance in 1. Multidrug resistance (resistance to at least isoniazid and rifampicin) was detected in 10 patients. In logistic-regression analysis, primary drug resistance was associated with radiological advanced tuberculosis ($p < 0.001$). **Conclusion:** Primary resistance to one or more drugs used in treating tuberculosis is relatively high. It is necessary to regularly screen for and treat drug resistance among those who live in close quarters, such

as army barracks, school dormitories and prisons. Regular surveillance of drug sensitivity patterns should be maintained to determine appropriate alternate drug regimens and detect the spread of resistant strains in the population.

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Introduction

Tuberculosis (TB) is one of the oldest known diseases in the world. It has been recognized for 116 years and effective chemotherapeutic regimens have existed for 54 years. Though it had remained a challenge for developing countries, industrialized countries had partly solved the TB problem. However, partly due to AIDS and mass population movements, TB has again emerged as a serious global public health issue. A case of pulmonary TB can infect 2–3 individuals in developed countries and 3–5 individuals in developing countries before a diagnosis is made [1].

The emergence of drug-resistant tuberculosis (DR-TB), especially multidrug-resistant tuberculosis (MDR-TB), poses a major threat to the control and prevention of TB [2–4]. It is known that the rate of primary resistance is approximately 5% or less in effective national programs, and 15% or more in newly implemented programs [5]. Previous reports from Turkey have shown high levels of primary and secondary drug resistance [6–8]. Because of this high degree of drug resistance, TB is easily transmit-

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ted within populations in close contact, such as the military. For this reason, we studied the prevalence of primary DR-TB and MDR-TB among military personnel and their dependents attending the Chest Diseases Hospital in Istanbul, Turkey.

Subjects and Methods

Subjects

Three hundred and sixty-five patients that were hospitalized in the Chest Diseases Clinic, Gata Camlica Chest Diseases Hospital between January 1999 and January 2000 with a diagnosis of pulmonary TB were included in the study. None of the patients had taken antituberculosis drugs previously.

Physical examination, routine hematological assessments and a purified protein-derived (PPD) skin test were performed for all cases. A PPD reaction of ≥ 10 mm of induration was classified as positive. The ELISA test for HIV antibodies (Abbott, HIV 1–2, USA) was also done. Pulmonary TB was radiologically classified as minimal, moderately advanced or far advanced [9]. Minimal lesions included those of slight to moderate density but which did not contain demonstrable cavitation. They may have involved a small part of one or both lungs, but the total extent regardless of distribution did not exceed the volume of lung on one side present above the second chondrosternal junction and the spine of the fourth or the body of the fifth thoracic vertebra. Moderately advanced lesions might have been present in one or both lungs, but the total extent did not exceed the following limits: disseminated lesions of slight to moderate density which may have extended throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one third the volume of one lung; total diameter of cavitation, if present, was less than 4 cm. Far advanced lesions were those more extensive than ‘moderately advanced’.

Our hospital serves as a center for military hospitals in western Turkey. Each year, approximately 2,500–3,000 patients are hospitalized with a diagnosis of any respiratory disease, including 1,000–1,200 cases of TB. It is compulsory to report cases of TB to the Tuberculosis Fighting Outpatient Clinic, Health Ministry, which launches investigations and provides necessary drugs to the patients. We use standard chemotherapy regimen and WHO guidelines for management of DR-TB [5].

Preparation of the Material

All sputum samples sent to the TB laboratory underwent decontamination and neutralization procedures with a 2% NaOH solution within 2 h, after which they were centrifuged with 3,000 rpm for 20 min and the supernatant discarded. The sediment was divided into two parts: one was stained using the Ziehl-Neelsen method and the smear examined. The other portion for culture was incubated with a Bactec 12B culture medium (Bactec 460, Becton Dickinson, Sparks, Md., USA) and left to grow. It was checked every 2 days during the 1st week and weekly afterwards. The final bacterial growth was determined at the end of the 6th week.

Identification and Drug Susceptibility Testing

A nitro alpha acetyl amino beta hydroxypropionophenone (NAP) test was used for the identification of mycobacterium. The isolate

Table 1. General features of patients with primary drug resistance

Features	Study population	Any drug resistance
Sex		
Female	13	4
Male	352	83
Age		
<25	253	63
25–44	84	17
45–64	19	5
≥ 65	9	2
Nonsmoker	127	30
Smoker	238	57
PPD test		
0–9 mm	61	6
≥ 10 mm	304	81
Chest X-ray		
Minimal	125	15
Moderately advanced	191	57
Far advanced	49	15
HIV		
Negative	365	87
Positive	0	0

was identified as *Mycobacterium tuberculosis* complex when the growth of mycobacterium was inhibited in the presence of NAP [10].

The antimicrobial susceptibility testing of *M. tuberculosis* complex isolates was performed by the indirect radiometric proportion method (Bactec). Antimicrobial agents tested against *M. tuberculosis* complex isolates and final drug concentrations with the Bactec 12B medium were as follows: isoniazid 0.1 $\mu\text{g/ml}$, rifampicin 2.0 $\mu\text{g/ml}$, streptomycin 2.0 $\mu\text{g/ml}$, and ethambutol 2.5 $\mu\text{g/ml}$ [10].

Statistical Analysis

All data are reported as mean $\pm$ SD. Multivariate logistic regression was performed to calculate odds ratios and 95% confidence intervals for risk quantification (sex, age, smoking, radiological appearance, PPD). All risk factors are presented as dichotomous variables. A value of $p < 0.05$ was considered significant for drug resistance to any of the four first-line drugs.

Results

Characteristics of Patients

Primary resistance to one or more drugs was detected in 87 (23.8%) patients: 83 were male and 4 were female, with a mean age of 25.5 ± 9.9 years (range, 19–71). Twelve patients with primary drug resistance were lost contacts and could not be followed up. Follow-up was possible for 75 patients (86.2%), of whom 73 (83.9%) recovered and 2 (2.3%) were unsuccessfully treated. Fifty-seven

Fig. 1. Antituberculosis drug resistance of cases.

Table 2. Patterns of drug resistance among 365 cases with primary *M. tuberculosis* infection

Isolates' response to drugs	Isolates	
	n	%
Resistance to one or more drugs	87	23.8
Resistance to one drug only	69	18.9
Isoniazid (INH)	37	10.1
Rifampicin (RIF)	1	0.3
Ethambutol (ETB)	27	7.4
Streptomycin (SM)	4	1.1
Resistance to two drugs only	11	3.0
INH + RIF	3	0.8
INH + ETB	5	1.3
INH + SM	2	0.6
SM + ETB	1	0.3
RIF + ETB	0	0
RIF + SM	0	0
Resistance to three drugs only	6	1.6
INH + RIF + ETB	5	1.3
INH + RIF + SM	1	0.3
INH + ETB + SM	0	0
RIF + ETB + SM	0	0
Resistance to all four drugs	1	0.3
INH + RIF + ETB + SM	1	0.3

cases with primary drug resistance involved cigarette smokers (65.5%). The mean PPD measurement was 15.7 ± 5.6 mm (range, 0–25); the PPD test was negative in 6 patients. Radiological examinations revealed that 72 cases were moderately or far advanced (table 1). All the patients were HIV-negative.

Drug Resistance

Resistance to a single drug was found to be most prevalent ($n = 69$) among the resistant patients. Two-drug resistance was noted in 11 patients, three-drug resistance in 6 patients, and four-drug resistance in 1 patient (table 2).

Resistance to isoniazid was most common, having been observed in 54 (14.8%) patients, followed by resistance to ethambutol 39 (10.7%), rifampicin in 11 (3%), and streptomycin in 9 (2.5%) (fig. 1). Multi-drug resistance (resistance to at least isoniazid and rifampicin) was detected in 10 patients. Six patients were cured, including 2 cases of probable cure. Two cases were considered as lost contacts, and for the other 2 cases, treatment was unsuccessful. The most important risk factor for drug resistance was radiological appearance ($p < 0.001$).

Discussion

The high primary drug resistance rate is a serious health problem in Turkey, as the incidence of TB is 30/100,000 [11]. The primary resistance rate has been shown to range from 16.6 to 26.6% [6, 12]. In this study, primary resistance was 23.8%, consistent with previous reports. A number of studies have reported isoniazid as the drug with the highest rate of resistance [13–17]. However, rifampicin [18], streptomycin [19–22], or ethambutol [23] have also been reported as having the highest incidence of resistance in some countries. In Turkey, it was found that isoniazid [7] and streptomycin [6] had the highest resistance figures. The reasons for these differences among countries could be due to variations in patient characteristics, general drug use, susceptibility test (Bactec, Löwenstein, etc.) methods, and the proportion of drug concentration.

In this study, ethambutol was associated with the second highest incidence of single-drug resistance, probably because it was the most commonly used. This resistance to ethambutol is of concern to treating physicians because streptomycin is autotoxic, nephrotoxic and is not used for older patients. Equally important, although resistance to rifampicin was observed in only 1 patient, it was involved in the MDR-TB of patients (table 2).

Although primary MDR-TB is reported to have an incidence of 0–54%, it is very hard to find and treat these cases [13–25]. In addition, the financial cost to treat these cases is high [26]. In this study, 10 patients had MDR-TB. Six of them were cured including two that were partially cured. Our cure rate (60%) was close to that reported by Tahaoglu et al. [27]. The successful management of MDR-TB cases will decrease the incidence of primary multidrug resistance in the population. Application of directly observed therapy (DOT) will help decrease MDR-TB and/or DR-TB cases [28].

It has been reported that characteristics such as age [27, 29, 30], sex [29, 30], race/ethnicity [30], and HIV

infection [15, 20, 30] are risk factors for drug resistance among TB patients. In this study, age, sex, smoking and PPD skin test were not considered significant risk factors for developing drug resistance. But there was a significant relationship between widespread radiological lesions on lung X-rays and drug resistance, probably because of the high number of bacilli in an advanced disease. Another probable explanation is that drug resistance is more common in cavitary lesions because they facilitate growth [31]. Another risk factor for drug resistance is bilateral disease at presentation, as reported by al Jarad et al. [32].

Conclusion

Because primary resistance to one or more drugs used in treating TB is relatively high, it is essential to regularly screen for and treat drug resistance among those who live in close quarters, such as army barracks, school dormitories and prisons. Regular surveillance of drug sensitivity patterns should be maintained to determine appropriate alternate drug regimens and detect the spread of resistant strains in the population.

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