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Original Article

A Report on Drug Resistance Patterns of *Mycobacterium tuberculosis* Isolates in Northern Iran

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Abstract

Background: There are limited data on the *Mycobacterium tuberculosis* (MTB) drug resistance in regions located at the proximity of the Caspian Sea. We aimed to assess the drug resistance patterns of the MTB isolates to anti-tuberculosis drugs in patients from four northern provinces of Iran between April 2013 and March 2019.

Methods: Drug susceptibility testing (DST) was performed by culturing MTB isolates on the Lowenstein-Jensen medium using the proportion method.

Results: Out of 963 MTB isolates, 927 (96.3%) were recovered from Iranian cases and 36 (3.7%) were from Afghan immigrants. Based on DST, 59 (6.1%) showed any drug resistance pattern, while 18 patients (1.9%) were multidrug-resistant (MDR) or rifampicin-resistant (RR). Resistance to streptomycin (STR), isoniazid (INZ), rifampicin (RIN), and ethambutol (ETL) was reported in 33 (3.4%), 28 (2.9%), 18 (1.9%), and 12 isolates (1.2%), respectively.

Conclusion: The rate of MDR/RR in four northern provinces of Iran was in line with previous reports from the World Health Organization. Due to proximity to the former Soviet Union, which had a high rate of MDR/RR isolates, the establishment of cross-border tuberculosis (TB) control strategies is recommended to reduce the possibility of MDR-TB transmission. Moreover, DST for all TB cases is recommended as an effective diagnostic tool for optimal monitoring and control of drug resistance in these areas. Future studies with a molecular epidemiology approach will be needed to evaluate the transmission dynamics of MTB in these regions.

Keywords: Iran, Multidrug Resistant, *Mycobacterium*, Tuberculosis

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Introduction

Mycobacterium tuberculosis (MTB), the causative agent of tuberculosis (TB), remains one of the top ten causes of death worldwide, especially in developing countries.[1] Epidemiological reports estimate an incidence rate of 10 million new TB cases, along with 1.5 million deaths in the world. Although the incidence of TB has decreased dramatically in recent years, the emergence of drug resistant TB, particularly rifampicin-resistant (RR) and multidrug-resistant (MDR) isolates, jeopardizes the disease control strategies.[2,3] Drug susceptibility testing (DST) is a method used for identification of MDR/RR-TB and helps the clinicians to choose effective therapeutic regimens. Annually, 3.4% of new cases diagnosed with TB are categorized as MDR/RR-TB, with the highest proportions in countries belonging to the former Soviet Union, such as the Russian Federation, Kazakhstan, Turkmenistan, and Azerbaijan.[1]

Iran is a developing country with a TB incidence of 14 per 100 000 population, and it neighbors Turkmenistan and Azerbaijan. According to the reports from the World Health Organization (WHO) in the year 2018, the rate of MDR/RR-TB was 1.3% in newly-diagnosed patients with TB in Iran.[1]

Although the patterns of MTB drug resistance have been previously reported from different regions of Iran, there were limited data on the northern provinces located at the proximity of the Caspian Sea. Here, we aimed to determine the resistance pattern of MTB isolates from new pulmonary TB cases in four provinces of Iran, including Golestan (high TB incidence in northeastern Iran), Guilan (northern Iran), Mazandaran (northern Iran), and Semnan (central part of Iran).

Materials and Methods

Settings

The Tuberculosis Reference laboratory (Gorgan, Iran) is a referral TB center for TB diagnosis and DST in northern regions of Iran, including Golestan, Mazandaran, Guilan, and Semnan provinces.

The Golestan province, in northern Iran, is located along the border with Turkmenistan, as well as Mazandaran and Semnan provinces.[4] This province has been reported as a high-TB incidence area (28 per 100 000 people).[3,5] The Mazandaran province (TB incidence: 10.7 per 100 000 people) is a historical and touristic region of Iran, located

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along the border with Tehran (capital of Iran), Guilan, Semnan and Golestan provinces.[4] The Guilan province (TB incidence: 10.3 per 100 000 people) is located in the north-western part of Iran, sharing a border with the Republic of Azerbaijan to the north, as well as the Mazandaran province to the east.[4,6] The Semnan province is located in the central region of Iran (TB incidence: 9.7 per 100 000 people), sharing a border with Golestan and Mazandaran to the north.[4]

Specimens and Data Collection

In this cross-sectional study, data from TB cases were gathered retrospectively between April 2013 and March 2019. The new-diagnosed culture positive cases with pulmonary TB were included. Patients with anti-TB treatment history, extra-pulmonary TB, non-tuberculous mycobacteria, negative culture, and without DST were excluded.

Clinical specimens were decontaminated by Petroff's method, subjected to smear microscopy and cultured by Ziehl-Neelsen method and Lowenstein-Jensen medium, respectively. The isolates were identified as MTB through assessment of the morphology of colonies, growth rate, pigment production, and conventional biochemical tests.[7,8] Demographic characteristics (age, sex, and nationality) were obtained from the Iranian TB Registry program. TB patients were divided into three age groups, including 1–29, 30–65, and > 65 years (Table 1).

Drug Susceptibility Testing

DST against rifampicin (RIN, 40 μg/mL), isoniazid (INZ, 0.2 μg/mL), ethambutol (ETL, 0.2 μg/mL), and streptomycin (STR, 4.0 μg/mL), was performed using the proportion method in the Lowenstein-Jensen media.[9] The MTB H37Rv strain was used for control of the DST procedure.

Definitions

A new case TB is a patient who has not had a treatment history for TB or has been treated for less than one month. Pan-susceptible was defined as MTB isolates that were susceptible to RIN, INZ, ETL and STR, while any-drug resistant isolate was defined as an isolate resistant to at least one of the mentioned drugs. Mono-drug resistant isolate was defined as an isolate resistant to only one of the first-line anti-TB drugs, whereas MDR was defined as the isolates that were simultaneously resistant to INZ and RIN.[9,10]

Statistical Analysis

Data analysis was performed using SPSS (version 16.0; SPSS, Chicago, IL). Descriptive analysis was conducted using frequencies with 95% confidence interval (CI). Association between the categorical variables was assessed using the Chi-square or Fisher's exact test, at the statistical significance level of 0.05.

Results

A total of 7122 pulmonary TB cases were identified, and 963 of them were included in this study. Most of the cases were from the Golestan province (n = 590, 61.3%), and the rest were from Mazandaran (n = 203, 21.1%), Guilan (n = 138, 14.3%), and Semnan (n = 32, 3.3%). The mean age of the patients was 46.5 ± 18.7 years, and 701 cases (72.8%) were male. Considering the age distribution of the studied population, 240 cases (24.9%) were under 30 years, 533 (55.4%) were 30–65 years old, and 190 were over 65 years of age. In terms of nationality, 927 cases (96.3%) were Iranian, 36 were Afghan immigrants, 34 (94.4%) were residents in Golestan, and 2 (5.6%) were from Mazandaran.

Drug Susceptibility Patterns

Among 963 MTB isolates, 59 isolates (6.1%, 95%

Table 1. Demographic Characteristics and Drug Resistance Profile of New Tuberculosis Case in Four Provinces of Iran

Characteristics		Drug Resistance Patterns					
		Mono Drug Resistance		Any Drug Resistance		Multidrug Resistance	
		n (%, 95% CI)	*P**	n (%, 95% CI)	*P**	n (%, 95% CI)	*P**
Age groups (y)	< 30	12 (5, 2.9–8.5)	0.61	14 (5.8, 3.5–9.6)	0.95	2 (0.8, 0.2–3)	0.79
	30–65	25 (4.7, 3.2–6.8)		34 (6.4, 4.6–8.8)		7 (1.3, 0.6–2.7)	
	> 65	6 (3.2, 1.5–6.7)		11 (5.8, 3.3–10.1)		3 (1.6, 0.5–4.5)	
Province	Golestan	27 (4.6, 3.2–6.6)	0.82	37 (6.3, 4.6–8.5)	0.6	7 (1.2, 0.6–2.4)	0.7
	Mazandaran	7 (3.4, 1.7–6.9)		9 (4.4, 2.4–8.2)		2 (1, 0.3–3.5)	
	Guilan	77 (5.1, 2.5–10.1)		10 (7.2, 4–12.8)		3 (2.2, 0.7–6.2)	
	Semnan	2 (6.3, 1.7–20.2)		3 (9.4, 3.2–24.2)		0 (0, 0–10.7)	
Gender	Male	30 (4.3, 3–6)	0.72	40 (5.7, 4.2–7.7)	0.22	4 (0.5, 0.2–1.5)	0.74
	Female	13 (5, 2.9–8.3)		19 (7.3, 4.7–11.1)		8 (3.1, 1.6–5.9)	
Nationality	Iranian	42 (4.5, 3.4–6.1)	0.51	58 (6.3, 4.9–8)	0.34	12 (1.3, 0.7–2.2)	0.63
	Non-Iranian	1 (2.8, 0.5–14.2)		1 (2.8, 0.5–14.2)		0 (0, 0–9.6)	
Total		43 (4.5, 3.3-6)		59 (6.1, 4.8–7.8)		12 (1.2, 0.7–2.2)	

*Based on Chi-square or Fisher exact test, whenever appropriate.

CI = 4.8%–7.8%) were resistant to at least one drug, including 58 Iranian and one from non-Iranian cases. Any-drug resistant isolates were common in Semnan (n = 3, 9.4%; 95% CI = 3.2%–24.2%), and relatively common in Guilan (n = 10, 7.2%; 95% CI = 4%–12.8%) and Golestan (n = 37, 6.3%; 95% CI = 4.6%–8.5%). As depicted in Table 2, the majority of any-drug resistant isolates were resistant to STR (n = 33, 3.4%; 95% CI = 2.5%–4.8%) followed by INZ (n = 28, 2.9%; 95% CI = 2%–4.2%). Also, 18 isolates (1.9%, 95% CI = 1.2%–2.9%) were identified as MDR/RR, and 43 (4.5%, 95% CI = 3.3%–6%) were mono-resistant (Table 1). In comparison with other provinces, the MDR profile was higher in patients from Guilan (n = 3, 2.2%; 95% CI = 0.7%–6.2%). The rate of MDR was lower in males than females; however, this difference was not statistically significant ($P = 0.74$). The resistance profile of MTB isolates was different across the four provinces; however, this discrepancy did not reach statistical significance ($P > 0.05$). In addition, more than half of isolates (7 out of 12, 58.3%) with MDR were found among those aged 30–65 old; however, this difference was not statistically significant ($P = 0.79$).

Discussion

As of the establishment of the TB control program in Iran, the incidence of TB was dramatically decreased from 34 to 14 per 100 000 individuals in 2019[1]; however, the emergence of drug-resistant MTB has threatened this program.[9]

We found that the MDR-TB rate was in accordance with those reported by the WHO and the Health Ministry of Iran.[1,3] In two studies previously conducted on MTB isolates from 21 and 5 provinces of Iran, the rate of MDR isolates were reported at 4.5% and 4.3%, respectively.[11,12] These percentages seem to be higher than our study that may be due to the recruitment of some TB patients with a history of anti-TB treatment. The identification of MDR-TB indicates the already circulating MDR isolates in the study area, which requires further enforcement of TB control strategies. In addition, recently, molecular studies were conducted in Iran, using Line probe assay, Xpert MTB/RIF assay, polymerase chain reaction (PCR) amplification and sequencing methods, which could be helpful for rapidly and accurately determining the DST for MTB isolates.[13-16]

This study revealed that more than half of MDR-TB cases and almost all Afghan cases were from the Golestan province. Besides, Guilan exhibited the highest rate of MDR-TB cases in this study. Every year, the Golestan province receives refugees from different parts of the country as well as neighboring countries, such as Turkmenistan and Afghanistan.[5] Golestan and Guilan have long borders with Turkmenistan and Azerbaijan, with 14% and 13% of MDR-TB cases, respectively.[1] The rate of MDR-TB in other countries around the Caspian Sea was reported to be 27% in Kazakhstan and 35% in the Russian Federation.[1] Immigration between neighboring countries may affect the rate of MDR-TB in Golestan and Guilan, although this hypothesis needs to be proven by further studies. Nevertheless, screening of immigrants at the border of entry is advised to reduce the possibility of MDR-TB transmission.

The any-drug resistance profile in MTB isolates was in agreement with lower values of previous reports from Iran, ranging from 10.2%–16.3%,[2,5,17,18] This could imply the possibility of initial resistance in MTB isolates in these areas. According to the reports of the WHO in 2018, TB incidence in Iran was lower than other neighboring countries, including Turkey, Armenia, Iraq, Turkmenistan, Azerbaijan, Afghanistan, and Pakistan, with 16–265 cases per 100 000 populations.[1] Thus, Iran had a lower number of cases that received anti-TB drugs, which could explain the low any-drug resistant isolates in Iran. As reported by other studies, different MTB genotypes may have different drug-resistance patterns,[19,20] therefore, further studies are warranted to investigate the main genotypes in Iran and neighboring countries.

We found that two-third of RIN resistant isolates were also resistant to INZ. A recent meta-analysis indicated that resistance to RIN could be regarded as a predictive marker for MDR-TB.[21] RIN is the most effective agent against MTB,[12] and the removal of this therapeutic agent has caused considerable implications for the treatment of patients, such as longer treatment courses, and the need for expensive drugs.

Drug resistance to STR had the highest proportion among the investigated drugs. Resistance to INZ had the second rank among those patients, and this finding is in line with previous reports from Iran.[2,22,23] Resistance to STR may be high due to cross-resistance with previous

Table 2. Resistance to First Line Drugs for *Mycobacterium tuberculosis* Isolated from Four Provinces of Iran

Type of resistance	Provinces				Total n (%, 95% CI)
	Golestan n (%, 95% CI)	Mazandaran n (%, 95% CI)	Guilan n (%, 95% CI)	Semnan n (%, 95% CI)	
Any Resistance to STR	24 (4.1, 2.7–6)	3 (1.5, 0.5–4.3)	5 (3.6, 1.6–8.2)	1 (3.1, 0.6–15.7)	33 (3.4, 2.5–4.8)
Any Resistance to INZ	16 (2.7, 1.7–4.4)	4 (2, 0.8–5)	6 (4.3, 2–9.2)	2 (6.3, 1.7–20.1)	28 (2.9, 2–4.2)
Any Resistance to ETL	10 (1.7, 0.9–3.1)	1 (0.5, 0.1–2.7)	1 (0.7, 0.1–4)	0 (0, 0–10.7)	12 (1.2, 0.7–2.2)
Any Resistance to RIN	10 (1.7, 0.9–3.1)	4 (2, 0.8–5)	3 (2.2, 0.7–6.2)	1 (3.1, 0.6–15.7)	18 (1.9, 1.2–2.9)
Pan-susceptible	553 (93.7, 91.5–95.4)	194 (95.6, 91.8–97.7)	128 (92.8, 87.2–96)	29 (90.6, 75.8–96.8)	904 (93.9, 92.2–95.2)

STR, streptomycin; INZ, isoniazid; ETL, ethambutol; RIN, rifampicin.

use of aminoglycosides. As STR is frequently prescribed for the treatment of TB as second line anti-TB drug and Category II therapy for patients with absence of treatment and relapse,[24,25] the high rate of resistance may lead to treatment failure. INZ-resistant MTB isolates are rapidly increasing worldwide,[26] which could result in extending the treatment course (up to 9 months). On the other hand, early diagnosis and treatment of INZ-resistant TB would be critical for prevention of the MDR-TB progression.

Resistance to RIN and INZ in the Mazandaran province was reported in previous studies.[12,27,28] However, they had a limited sample size and did not include ETL and STR in their study. The present study provides valuable insight into resistance to first-line anti-TB drugs in Mazandaran, which could be useful for TB control and management in this province.

The majority of TB cases were found in patients who were younger than 65 years. The high frequency of TB in young adults may indicate the occurrence of recent transmission, whereas this status in elderly individuals suggests the distant past acquisition of infection,[29] Hence, it seems that both mechanisms of transmission are responsible for the acquisition of TB in these studied areas.

To the best of our knowledge, the current study is the first to provide valuable insight into the pattern of drug resistance to MTB isolates from the Semnan province using the standard proportion method. Although RR and INZ-resistance are commonly detected in Semnan province, the profile of MDR-TB is rarely identified. Further studies using a larger sample size would be recommended for determining the drug resistance patterns for MTB isolates.

There are some limitations in our study; first, the number of studied MTB isolates for the Semnan province was too low to determine the precise patterns of drug resistance in this region. Second, we did not perform DST for second-line anti-TB drugs. Third, we did not identify the mutations corresponding to resistance to anti-TB drugs.

This study demonstrated comparative information about drug resistance patterns from the provinces located in the vicinity of the Caspian Sea. DST is one of the most effective tools for seeking the optimal treatment choice and the control of TB. The prevalence of drug-resistant MTB in these studied areas was in agreement with previous reports from the WHO. The presence of MDR isolates in these regions warns that these areas need special attention from health officials. Immigration from neighboring countries with a high rate of MDR-TB could be a predisposing factor for the incidence of drug-resistant isolates in Iran. Therefore, screening all Iranian and non-Iranian immigrants, establishing advanced diagnostic tools at entry borders of Iran, is recommended.

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Authors' Contribution

NM: Research design, writing original draft, review and editing. BP: Methodology and data analysis. MA: Investigation and data collection.

Conflict of Interest Disclosures

The authors report no conflict of interest.

Ethical Statement

This project is vetted by the Ethics Committee of Golestan University of Medical Sciences (IR.GOUMS.1398.198), and was supported by the Golestan University of Medical Sciences (grant # 110945).

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