MEDICAL SCIENCE MONITOR

PUBLIC HEALTH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 1313-1318
DOI: 10.12659/MSM.892951

Received: 2014.11.04
Accepted: 2015.01.02
Published: 2015.05.07

Correlations between Drug Resistance of Beijing/W Lineage Clinical Isolates of *Mycobacterium tuberculosis* and Sublineages: A 2009–2013 Prospective Study in Xinjiang Province, China

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Source of support: The Study was funded by National Natural Science Foundation of China (81172662) and High Education Doctoral Program of Chinese Ministry (20123706110004)

Background: The prevalence of drug-resistant tuberculosis (TB) in Xinjiang is higher than in other regions of China, and Beijing/W lineage *Mycobacterium tuberculosis* (MTB) is the dominant strain of MTB in Xinjiang. However, information on multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, particularly the correlation between MDR and the Beijing/W lineage and the correlation between drug resistance and the Beijing/W sublineage strains, is limited.

Material/Methods: We conducted a prospective study to describe the prevalence of MDR/XDR TB, Beijing/W lineage and sublineage strains in Xinjiang in China from 2009 to 2013. All MTB underwent drug susceptibility testing to the first- and second-line anti-tuberculosis drugs. The Beijing/W lineages and sublineages were detected by large-sequence polymorphisms with polymerase chain reaction.

Results: A total of 410 clinical isolates were identified. The overall percentage of MDR and XDR cases in Xinjiang was 13.2% (54/410) and 13.0% (7/54), respectively. Overall, 9.8% (14/143) of the Beijing lineage MTB were MDR patients, and 15.6% (40/257) of the Non-Beijing lineage MTB were MDR patients. In the 143 Beijing MTB lineages, 11.2% isolates were in sublineage 105, 15.4% isolates were in sublineage 207, 69.2% isolates were in sublineage 181, and 4.2% isolates were in sublineage 150. None of the isolates were detected in sublineage 142. Significant differences between the Beijing/W and non-Beijing/W strains were observed regarding INH and EMB resistance, respectively.

Conclusions: The prevalence of the MDR TB in Xinjiang remains high and imposes challenges for TB control. Four Beijing/W sublineage isolates were observed in Xinjiang. There was no correlation between MDR and the Beijing/W lineage and no correlation between drug resistance and the Beijing/W sublineage strains. Surveillance of the clinical isolates of MTB is recommended to strengthen the identification of MDR/XDR TB and sublineages of the Beijing/W strains.

MeSH Keywords: Drug Resistance • *Mycobacterium tuberculosis* • Sprains and Strains

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892951

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Background

Based on the Bulletin of the World Health Organization (WHO), one-third of the world's population may be asymptomatically infected with tuberculosis (TB) [1]. The occurrence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB challenges disease control and creates a more complex situation, particularly because XDR TB is a mostly incurable form with a rate of 15% among the MDR strains reported in 58 countries[2,3]. TB has been a remarkable public health issue in mainland China, and 80% of new TB cases worldwide have been reported in China each year. TB prevalence has decreased by 30% due to the DOT's plan [1,4]. Nevertheless, the drug susceptibility tests for *Mycobacterium tuberculosis* (MTB) isolates showed that 8.3% of pulmonary TB patients had MDR TB [5,6]. The second highest incidence of TB (464/100 000) among all provincial regions in China occurred in the Xinjiang Uygur Autonomous Region (Xinjiang, for short). Differences in TB incidence have been observed in China [6–8]. However, information on the drug-resistance and prevalence of MDR/XDR TB in Xinjiang province has been limited since 2009.

MTB has been classified into six major lineages using large sequence polymorphisms (LSPs) [9]. Each lineage is strongly correlated with specific geographic populations [10]. Beijing/W strains are detected using several LSPs with genomic microarray approaches and then subdivided into five sublineages by specific regions of difference (RDs) [11]. The RD105 region is one LSP and a marker that can differentiate Beijing/W lineage strains from non-Beijing/W lineage strains [10]. RD142, RD150, and RD181 regions are variably deleted in Beijing/W lineage strains [12]. Beijing/W strains are the dominant strains in China. However, the reports analyzing the subdivisions of the Beijing/W lineage by LSPs methods and exploring the correlation between drug resistance and Beijing/W lineage in China are scarce [13]. From January 2009 to December 2013, we estimated the prevalence of MDR/XDR TB to investigate the drug-resistant profiles of TB in Xinjiang, China. By classifying the Beijing/W strains of these MTBs, we attempted to investigate the drug susceptibility patterns of the sublineages of Beijing/W lineage strains and determine the relationships between the drug resistance of epidemic MTB and the sublineages of Beijing/W lineage strains.

Material and Methods

Collection and isolates of clinical sputum specimens

To fully reflect the prevalence of TB in Xinjiang, the entire region was divided into two regions: the northern area and the southern area. From January 2009 to December 2013, sputum specimens were collected from suspected pulmonary TB patients at Xinjiang Uygur Autonomous Region People's Hospital and Xinjiang Uygur Autonomous Region Chest Hospital (both located in the northern area) and Kashi People's Hospital and Kashi Center for Disease Control and Prevention (both located in the southern area). All patients were suspected of having pulmonary TB based on the guidelines for TB diagnosis and were treated in local Chest Hospitals. Three sputum samples from each patient were collected. Additionally, a questionnaire including information such as sex, age, birth place, previous history of TB, recent smear-positive sputum tests, and current address was completed.

The study was approved by the Ethics Committee of Xinjiang Uygur Autonomous Region People's Hospital and the Ethics Committee of Xinjiang Uygur Autonomous Region Chest Hospital. Written informed consent was signed by individuals or by the parents of children before enrollment in the study.

The sputum cultures and drug susceptibility tests for strains were performed based on the TB diagnosis bacteriology test criteria of the Chinese Anti-tuberculosis Association. Positive samples were then evaluated by employing the Mycobacterial Growth Indicator Tube 960 broth system culture (MGIT, Becton Dickinson, Franklin Lakes, USA) using the following concentrations: 4 first line anti-TB drugs, isoniazid (INH) 0.2 μg/ml, rifampin (RFP) 1.0 μg/ml, streptomycin (SM) 2.0 μg/ml, ethambutol (EMB) 7.5 μg/ml; and 7 second line anti-TB drugs, ofloxacin (Ofx) 2.0 μg/ml, capreomycin (Cm) 20.0 μg/ml, kanamycin (Km) 30.0 μg/ml, amikacin (Am) 40.0 μg/ml, paminosalicylic acid (PAS) 2.0 μg/ml, ethionamide (Eto) 40.0 μg/ml and cycloserine (Cs) 40.0 μg/ml. Isolates were considered resistant to a particular drug if the growth rate was more than 1% compared with the control or sensitive if the growth rate was less than 1% compared with the control [7,14]. The definition of MDR TB is a strain that is resistant to at least two first-line drugs (INH and RFP). XDR TB is a strain that is resistant to INH and RFP in addition to any fluoroquinolone and at least one of the injectable second-line drugs (Am, Cm, or Km) [2].

Identification of MTB isolates and genomic deletions using PCR and multiplex PCR

Mycobacterial genomic DNA was extracted from colonies growing on medium [15]. Polymerase chain reaction (PCR) amplification of the 16S rRNA and MTP40 genes was used for the molecular identification of the mycobacterial isolates, as described in previous studies[7,15]. Subpopulation structure of the MTB Beijing/W lineage strains was identified using both PCR and multiplex PCR. The RD105 LSP was used to identify the Beijing/W lineage strains [12]. The designed primers and detailed steps of PCR experiments have been described elsewhere [7,16]. The PCR products of the specimens from each sublineage for DNA sequencing were selected randomly.

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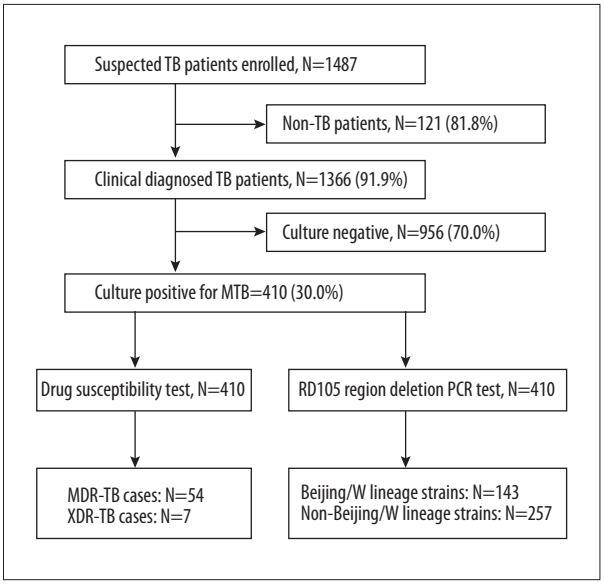

Figure 1. Flowchart of eligible suspected tuberculosis (TB) patients in Xinjiang, China, from 2009 to 2013.

Statistical analysis

Pearson's χ^2 test with significance level of 0.05 was used for the analysis. Fisher Exact test was used if the assumption of Pearson's χ^2 test was not met. And Fisher's exact test must meet the assumption of fixed marginal distributions when applied. The R 2.10.0 statistical software was used for the analysis [17].

Results

Characteristics of Non-MDR, MDR, and XDR patients

A total of 1487 suspected TB patients were enrolled in our study between January 2009 and December 2013. Of these clinically diagnosed 1366 TB patients (91.9%) who provided their sputa for MTB, 410 (30.0%) had a positive culture, and 956 (70.0%) had a negative culture. Finally, the positive sputa of the 410 patients were analyzed using both the drug susceptibility test and RD105 region deletion PCR test. A flow chart of this study is shown in Figure 1.

The mean age of the 410 patients was 39.8 years, with a range from 5 to 74 years. The percentage of males and females was 46.1% and 57.2%, respectively; further, 72.2% of the patients were inpatients, and 43.7% were newly diagnosed cases. No significant difference was observed between Non-MDR and MDR stratified by sex and TB treatment; however, significant differences were found between Non-MDR and MDR stratified by age groups and patient types (Table 1).

Drug resistance in Beijing/W lineage MTB and non-Beijing/W lineage

According to the RD105 region deletion PCR test, 143 isolates contained the RD105 region deletion and were therefore classified as Beijing/W lineage strains, and 257 isolates without the RD105 region deletion were classified as non-Beijing/W lineage strains (Table 2). Additionally, 9.8% (14/143) of Beijing lineage MTB were MDR patients, and 15.6% (40/257) of Non-Beijing lineage MTB were MDR patients. No significant difference between the Beijing/W and non-Beijing/W strains was observed regarding FRP, SM, and MDR resistance. However, significant differences between the Beijing/W strains and non-Beijing/W strains were observed regarding INH and EMB resistance.

Isolates in various sublineages within Beijing/W lineage MTB

Within the 143 Beijing/W isolates, 11.2% (16/143) were identified as sublineage RD105, with only the RD105 region deletion detected. Additionally, 15.4% were identified as sublineage RD207 with concurrent deletions of RD105 and RD207 regions; 69.2% were identified as sublineage RD181 with concurrent deletions of RD105, RD207 and RD181 regions; and 4.2% were identified as sublineage RD150 with concurrent deletions of RD105, RD207, RD181, and RD150 regions. The RD142 region deletion was not detected in all the 143 isolates. Drug resistance in the sublineages of Beijing lineage strains can be observed in Table 3. No significant difference was found between drug resistance (INH, RFP, SM, EMB, and MDR) and sublineages of Beijing strains.

Discussion

The prevalence and drug resistance of TB in Xinjiang are higher compared with other regions of China. The surveillance of drug resistance in Xinjiang is also important for effectively controlling TB in the entire region [8]. As the Bulletin of the WHO on drug-resistant MTB in China has stated, the proportions of overall drug resistance (26%), drug resistance in new cases (26%), and retreated smear positive cases (31%) in Xinjiang were relatively high, and the MDR prevalence was approximately 5% [8]. In the 5 years of surveillance since 2009, the overall MDR, MDR in new cases, and MDR in retreated smear positive cases in Xinjiang were 13.2% (54/410), 12.9% (23/178), 13.4% (31/232), respectively, which were all significantly higher compared with the WHO's report. Furthermore, overall drug resistance was also higher than the national MDR surveillance data (8.3%) and the estimated prevalence of MDR (5.3%), according to a review of drug-resistant TB in China [18]. Qi et al. reported that the prevalence of MDR in Xinjiang was 14.1%, which was similar to the 13.2% in our study showed [8].

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Table 1. Characteristics of Non-MDR/XDR, MDR and XDR TB patients in Xinjiang, China, among 2009–2013.

Characteristics	Non-MDR (N=356)	MDR (N=54)	XDR (N=7)	P values*
Sex				
Male	168 (87.0)	25 (13.0)	3 (1.6)	χ^2=0.015, P=0.902
Female	188 (86.6)	29 (13.4)	4 (1.8)	
Age group				
<20	29 (85.3)	5 (14.7)	0 (0.0)	
20–29	103 (93.6)	7 (6.4)	0 (0.0)	
30–39	72 (86.7)	11 (13.3)	2 (2.4)	χ^2=11.747, P=0.038
40–49	55 (85.9)	9 (14.1)	1 (1.6)	
50–59	33 (73.3)	12 (26.7)	2 (4.4)	
≥60	64 (86.5)	10 (13.5)	2 (2.7)	
Patients' type				
Inpatients	241 (83.1)	49 (16.9)	6 (2.1)	χ^2=12.027, P=0.001
Outpatients	115 (95.8)	5 (4.2)	1 (0.8)	
TB treatment				
New	155 (87.1)	23 (12.9)	1 (0.6)	χ^2=2.623, P=0.105
Retreatment	201 (86.6)	31 (13.4)	6 (2.6)	

* Non-MDR *vs.* MDR(N=54).

Table 2. Drug resistance in Beijing lineage MTB and non-Beijing lineage MTB in Xinjiang, China, among 2009–2013.

Drug resistance	Total No. isolates (N=410)	Beijing lineage MTB (N=143)	Non-Beijing lineage MTB (N=257)	P values
INH	84	19	65	χ^2=7.982, P=0.005
RFP	56	15	41	χ^2=2.278, P=0.131
SM	92	25	67	χ^2=3.826, P=0.050
EMB	61	8	53	χ^2=16.055, P<0.001
MDR	54	14	40	χ^2=0.238, P=0.265

Table 3. Drug resistance in different sublineages of Beijing strains in Xinjiang, China, among 2009–2013.

Drug resistance	RD105 (N=16)	RD207 (N=22)	RD181 (N=99)	RD150 (N=6)	P values*
INH (N=19)	2	5	12	0	P=0.533
RFP(N=14)	2	3	9	0	P=0.743
SM (N=25)	3	6	16	0	P=0.460
EMB (N=8)	2	1	5	0	P=0.583
MDR (N=14)	1	2	11	0	P=1.000

* Fisher Exact test was used.

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XDR TB has been spread worldwide, and it has been reported that the prevalence of XDR TB among MDR TB cases is approximately 6.6–23.7% worldwide [1,2]. The information on XDR TB is essential to treating and controlling TB [19]. Recent surveillance data in the eastern area of China have shown that the XDR TB cases accounted for 6.3–18.7% of MDR TB cases [20–23]. Qi et al. reported that the prevalence of XDR in Chinese Han population was 9.6% [8]. This study showed that the prevalence of XDR TB in Xinjiang was relatively high, at 13.0% (7/54). The various ethnic group characteristics, such as life habits, genetic background, and drug metabolism, may account for this difference.

In considering MDR TB prevalence in various age groups, a significant difference was observed between age groups (P=0.038), but no increased or decreased tendency of MDR TB prevalence with ages was found (CMH P=0.071), similar to a previous report in the Japanese population[24]. However, some studies have shown that the prevalence of MDR in the Chinese Han population increased with older age [14]. The prevalence of MDR in the newly diagnosed and retreated cases was 12.9% and 13.4%, respectively, with no significant difference, indicating the high prevalence of MDR and the high burden of drug-resistant TB cases in Xinjiang, China.

There were some valuable studies that showed that Beijing/W lineage strains might be correlated with drug resistance, particularly MDR, and that Beijing/W lineage strains had a significantly higher MDR TB prevalence compared with non-Beijing/W lineage strains [12,25,26]. The data in our study revealed a relatively high prevalence of MDR TB in Xinjiang but did not demonstrate any significant association between MDR TB and Beijing/W lineage. However, a significant correlation between drug resistance (only INH and EMB) and Beijing/W lineage was found (Table 2). In other words, INH /EMB drug resistance is negatively correlated with the Beijing/W lineage. The drug resistance rate of INH/EMB was significantly lower in the Beijing/W lineage compared with the non-Beijing/W lineage. This result may imply that INH and EMB are preferentially chosen for treating non-Beijing/W lineage TB patients, and both INH and EMB may be given priority to treat Beijing/W TB patients in Xinjiang. This finding may be helpful for the future treatment of TB patients in Xinjiang.

To further explore the correlation between drug resistance and Beijing/W strains, the MTB isolates were then divided into 4 sublineages (RD105, RD207, RD181, and RD150) by LSPs. No isolate with RD142 region deletion was detected. Similarly, reports in other countries have shown that the collected isolates did not have the RD142 region deletion [27,28]. However, a study conducted in Beijing showed that 26.4% of Beijing/W lineage strains belonged to sublineage 142 [22], and another study showed that 33.0% of Beijing/W lineage strains belonged to sublineage 142 [29]. Currently, the function of sublineage 142 is still being questioned. Due to the low isolate numbers of sublineage 142, it may be less pathogenic [13], and it may be an important virulence factor for a fraction of the Beijing/W lineage isolates and associated with extra-pulmonary TB [30]. Recent reports have shown that the numbers of sublineage 150 were the second highest of the top 5 sublineages of Beijing/W lineage [13,16], and sublineage 150 may also be correlated with extra-pulmonary TB [30]. In this study, the proportion of sublineage 181 strains was 69.2% (99/143), similar to reports in the USA (sublineage 181, 64.4%) and China (sublineage 181, 88.7%) [16, 30]. All of the studies have indicated that the pulmonary TB patients of sublineage 181 may represent the sporadic cases.

In our study, there was no significant correlation between drug resistance and the sublineages of Beijing/W lineage (Table 3). Similar results have been demonstrated in previous studies [7,14]. One study attributed this lack of relationship to the small sample size of sublineages 150 and 142, which may be related to drug resistance and pathogenicity [7]. However, Beijing/W lineage strains were generally considered to be correlated with nosocomial infections, community outbreaks, and drug resistance [12,30,31]. Therefore, it is still necessary to collect more samples of clinical isolates to explore the correlation between drug resistance and Beijing/W lineage sublineages in Xinjiang. Molecular epidemiological methods should also be used to recognize potential outbreaks of drug-resistant isolates.

There were some limitations of the study. First, the data used in the study were collected from clinical isolated MTB. However, the hospitals involved in this study are the largest general and specialized hospitals in the region, and more than 90% of patients were from the hospitals mentioned in this study based on our surveillance in recent years. Second, although no selection bias was detected on the demographic characteristics of the patients, there was a higher inclusion rate of serious TB cases in this region, which may have caused an overestimation of drug-resistant TB.

Conclusions

The prevalence of MDR TB in Xinjiang province was high and creates challenges in the control of TB. There were no correlations between MDR and Beijing/W strains or between drug resistance and the sublineages of Beijing/W strains. However, significant differences between Beijing/W strains and non-Beijing/W strains were observed regarding INH and EMB resistance.

Surveillance on the clinical isolates of MTB is recommended to strengthen the identification of MDR/XDR TB and sublineages of Beijing/W strains.

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