



Original Research Article

Prevalence of multi-drug resistant (MDR) pulmonary tuberculosis in a tertiary care rural hospital in Western Maharashtra, India



Snehal Patil¹, Prasanna Nakate^{1,*}, Suvarna Patil¹, Yogendra Shelke¹

¹Dept. of Microbiology, BKL Walawalkar Rural Medical College, Ratnagiri, Maharashtra, India

ARTICLE INFO

Article history:

Received 02-06-2019

Accepted 07-08-2019

Available online 09-09-2019

Keywords:

Tuberculosis (TB)

Multidrug resistant tuberculosis

(MDR-TB)

GeneXpert assay

Rifampicin resistance

M tuberculosis

ABSTRACT

Introduction: The emergence of Multi-Drug Resistant tuberculosis (MDR-TB) has become a big issue in tuberculosis (TB) control programs in recent times. It is seen more frequently in patients already treated for TB, but has been now diagnosed in new TB patients as a primary infection. Present study was carried out to find out the prevalence of MDR-TB in new and previously treated pulmonary TB patients attending a tertiary care rural hospital.

Material and Methods: The study included a total of 1154 suspected MDR-TB patients out of which 1052 were new patients while 102 had received anti-TB drugs in past. Sputum samples of these patients were tested using GeneXpert MTB/RIF assay to detect *Mycobacterium tuberculosis* infection and Rifampicin resistance.

Results: MDR-TB was detected in 5.55% of overall patients. In case of new TB suspects, MDR-TB was detected in 4.37%, while 17.65% of patients with past history of anti-TB treatment had MDR-TB.

Conclusion: Improper management of drug sensitive TB has led to emergence of MDR-TB. Previous drug treatment seems to be the most important risk factor for acquiring resistance. It is important to strongly suspect and correctly diagnose MDR-TB at an early stage in all suspected patients of tuberculosis to control the spread of this disease and for improving the management of all TB cases.

© 2019 Published by Innovative Publication.

1. Introduction

Tuberculosis (TB) continues to be a major health issue worldwide even after great efforts being taken for its control and prevention. Although Lung is the commonest site affected in TB, it can also affect other organ systems presenting as an extra-pulmonary TB. In pulmonary TB, the patients often present with an insidious clinical onset with symptoms such as lack of appetite, low-grade evening fevers, and night sweats. Respiratory symptoms such as cough which is initially dry and later on productive with purulent or mucous expectoration also develop. Hemoptysis and chest pain can also occur.¹

Infection with TB bacillus is found in almost 1/3rd of world's population and every day nearly 5000 new cases are being added to this.² According to the 2017 Global TB report, in India the incidence of TB was found to be

approximately 28,00,000 cases which accounts for 1/4th of total TB cases in the world.³ India reports 1.9 million new cases of TB each year. Out of these, 0.8 million are open cases of TB with sputum smear positive for acid fast TB bacilli and have all the potential to infect their contacts.⁴ As per the World Health Organisation (WHO), in India the death rate due to TB is nearly 28 per 100,000 population which is highest among all other communicable diseases and accounts for 26% of all avoidable adult deaths.⁴

Although the WHO and governments across the world are taking great efforts for prevention and control of TB, the emergence and spread of Multi-drug resistant strains of TB bacillus has become a big hurdle in TB control programs. Presently MDR-TB is defined as resistance of TB bacilli to at least Rifampicin and Isoniazid (INH) which are the most important primary drugs used to treat TB, with or without resistance to other anti-tubercular drugs.⁵ In 2016, multi-drug resistance was diagnosed in 3.9% of new patients of TB, whereas in patients who were treated

* Corresponding author.

E-mail address: prasannanakate@gmail.com (P. Nakate).

for TB in past with primary drugs, it was detected in 21% cases according to the Global TB Report.⁵ In the same year (2016) in India, the prevalence of MDR-TB was found to be 2.5% and 16% among new and previously treated patients respectively.⁵ The data from Revised National Tuberculosis Control Program (RNTCP) TB Status report for years 2015, 2016 and 2017 suggests that the number of MDR-TB cases are gradually increasing in India.² Inappropriate management of both drug sensitive as well as resistant TB cases has resulted in emergence of mutant TB bacilli acquiring resistance to primary drugs. Although the drug sensitive TB can be effectively cured with primary drugs, it is very difficult to treat MDR-TB. Treatment of MDR-TB requires long duration as compared to the Directly Observed Treatment Shortcourse (DOTS) chemotherapy used for drug sensitive TB. It is costly and contains drugs which are potentially toxic with more side effects. Although MDR-TB occurs more frequently in patients who have already taken primary anti TB drugs in past, it is now slowly being reported from new TB suspected patients. If not controlled, it may replace all the drug sensitive population of TB bacilli and primary anti-TB drugs will become totally ineffective. Further, the drug resistance can become more extensive involving those drugs which are used to treat MDR-TB leading to Extensively Drug Resistant tuberculosis (XDR-TB). The Centre for Disease Control and Prevention (CDC) introduced the concept of XDR-TB in March 2005 for the first time.⁶ It is now defined as cases of tuberculosis resistant to Isoniazid and Rifampicin along with resistance to one of the fluoroquinolones (Ofloxacin, Levofloxacin or Moxifloxacin) and one of the injectable drugs (Kanamycin, Kapreomycin or Amikacin) which are drugs used to treat MDR-TB.⁷ With early detection and appropriate treatment with second line anti-tubercular drugs, MDR-TB can be treated and emergence of XDR-TB can be prevented. With this background, the present study was conducted in a tertiary care rural hospital to find out the prevalence of multi-drug resistant pulmonary tuberculosis (MDR- TB) in all suspected patients (new as well as those patients who received anti-tubercular treatment in past).

2. Material and Methods

This prospective study was conducted in a tertiary care rural teaching hospital in rural part of western Maharashtra from January 2018 to April 2019. The study was approved by the Institutional ethics committee. Overall 1154 sputum smear positive as well as negative patients suspected to have drug resistant pulmonary tuberculosis were included in the study irrespective of age, sex and HIV status. Out of these, 1052 were new patients and 102 were previously treated patients. Morning sputum samples were collected from these patients after giving proper instructions so as to obtain good quality sputum in a Falcon tube of 50 ml capacity. The samples were tested for detection of *Mycobacterium tuberculosis*

and Rifampicin resistance using GeneXpert MTB/RIF assay. This method is more sensitive in detecting presence of TB bacilli in sputum samples than just smear and microscopic examination. It can detect both *Mycobacterium tuberculosis* DNA and genetic mutations associated with Rifampicin resistance simultaneously in a short span of just two hours using sputum samples.⁸ Though conventional culture based drug sensitivity testing is considered as a gold standard investigation to detect MDR, the sensitivity and specificity of GeneXpert MTB/RIF assay is comparable with conventional methods.⁹ GeneXpert MTB/RIF assay is a fully automated cartridge based molecular diagnostic test for TB. In this assay, about 3–5 ml of sputum sample is mixed with twice the volume of sample reagent. It is shaken vigorously and incubated at room temperature for 10 minutes. After 10 minutes it is again shaken vigorously and incubated for another 5 minutes. 2 ml of this processed sample is then added to GeneXpert cartridge which is then loaded in the device. The results are finally interpreted by the GeneXpert system based on fluorescent signals which are displayed on the system monitor after about 90 minutes.⁹ This test has an advantage of short turnaround time, which makes it extremely useful for diagnosis of MDR-TB in a country like India with great burden of TB. Resistance only to Rifampicin (monoresistance) is very rare and almost all Rifampicin-resistant strains of TB bacilli are also resistant to other primary drugs, especially to Isoniazid. For this reason, Rifampicin resistance is considered as a surrogate marker for MDR-TB.¹⁰ In the present study, the patients whose sputum sample showed positive results for *M. tuberculosis* by GeneXpert assay were considered as confirmed pulmonary TB cases. The samples showing additional result as Rifampicin resistance detected were considered as multi-drug resistant TB cases.

3. Results

During the study period, a total number of 1154 sputum samples from suspected drug resistant pulmonary TB patients (new as well as previously treated) were tested by GeneXpert assay irrespective of their age, sex and HIV status. Out of this, 357(30.94%) patients were tested positive for TB. Rifampicin resistance was detected in 64(5.55%) patients while 293(25.39%) patients had drug sensitive TB. The details of GeneXpert testing with distribution of MDR-TB in all suspected patients is shown in Figure 1.

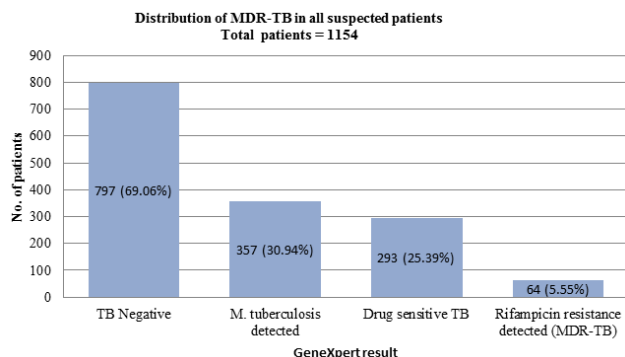
Out of the total patients, 1052 were new patients, without any past history of TB or antitubercular drug treatment. 306(29.09%) of these new patients were detected as TB positive by GeneXpert assay and Rifampicin resistance was detected in 46(4.37 %) patients. 260(24.72%) patients had infection with drug sensitive TB bacilli. Table 1 shows the details of GeneXpert testing with distribution of MDR-TB in these newly suspected patients.

Table 1: Distribution of MDR-TB in new patients

Total patients	TB Negative	<i>M. tuberculosis</i> detected	Drug sensitive TB	Rifampicin resistance detected (MDR-TB)
1052	746(70.91%)	306(29.09%)	260(24.72%)	46(4.37%)

Table 2: Distribution of MDR- TB in previously treated patients

Total patients	TB Negative	<i>M. tuberculosis</i> detected	Drug sensitive TB	Rifampicin resistance detected (MDR-TB)
102	51(50%)	51(50%)	33(32.35%)	18(17.65%)

**Fig. 1:** Distribution of MDR-TB in all suspected patients

102 patients in this study were previously treated with anti-tubercular drugs and were suspected to have MDR-TB. Of these, *M. tuberculosis* was detected in sputum samples of 51(50%) patients. Rifampicin resistance was detected in 18(17.65%) of these isolates whereas 33(32.35%) isolates were sensitive to Rifampicin. The detailed result of GeneXpert testing with distribution of MDR-TB in these previously treated patients is shown in Table 2.

4. Discussion

MDR-TB occurs because of development of resistance by *Mycobacterium tuberculosis* to both rifampicin and isoniazid with or without resistance to other anti-TB drugs.⁵ The molecular mechanisms of resistance to these two drugs are now largely understood. Rifampicin acts on *Mycobacterium tuberculosis* by binding to the β -subunit of the RNA polymerase, inhibiting the elongation of messenger RNA.¹¹ Resistance to rifampicin is developed due to mutations in the *rpoB* gene that codes for the β -subunit of the RNA polymerase. This results in conformational changes causing decreased affinity for the drug with development of resistance.¹² The Mechanism of action of isoniazid is inhibition of synthesis of mycolic acids in mycobacteria through the NADH-dependent enoyl-acyl carrier protein (ACP)-reductase, encoded by *inhA* gene.¹⁰ Isoniazid resistance is associated with mutations in genes *katG* and *inhA* or its promoter region.¹⁰

Multi-drug resistant tuberculosis, to a large extent a man-made problem, has emerged because of poor management of drug sensitive TB. Many new cases of MDR-TB are created each year because of multiple associated factors which include errors by treating physicians such as prescribing inappropriate or inadequate medications, poor compliance from patients, issues related to availability of drugs and many more. Because of this, TB bacilli which were initially fully susceptible to primary drugs develop spontaneous genetic mutations and acquire resistance.¹³ The treatment of MDR-TB is costly, complicated and difficult. Though the drug resistant strains arise more commonly in patients who have been previously treated, sometimes they can cause primary infection in new patients without any prior history of TB. Therefore it is important not only to diagnose TB in a suspected patient, but also to detect multi drug resistance at first place. The availability of GeneXpert has revolutionised TB diagnostic services in recent times. This technique is more sensitive than smear examination alone for TB diagnosis and it also detects Rifampicin resistance in just 2 hours.

In the present study, MDR-TB was diagnosed in 5.55 % of overall MDR suspect patients using GeneXpert. In a study carried out by Bansal SK et al the MDR-TB prevalence was reported to be 6.3% in overall MDR suspects.¹⁴ In case of new patients who never had past history of TB or antitubercular drug treatment, MDR-TB was detected in only 4.37% cases in our study. On the other hand, 17.65 % of previously treated patients were diagnosed to have MDR-TB. Almost similar findings were recorded in global estimates of TB in 2016, where 4.1% of newly suspected and 19% of previously treated TB cases were MDR.¹⁵ Bansal SK et al have reported the prevalence of M DRTB as 1.9% in new cases and 10% in previously treated cases.¹⁴ According to a multicentre study conducted in different parts of North India, the prevalence of MDR-TB was recorded as 9% in newly diagnosed cases of pulmonary TB which is higher than global prevalence rate of 3% – 5%.² In one more study conducted in Punjab, 26% of newly diagnosed TB patients were found to have MDR-TB showing very high burden of drug resistant TB in the area.¹⁶ In another study conducted by Sethi S et al, MDR-TB was found in 9.9% of newly diagnosed and 27.6% of previously treated patients.¹⁷ According to the first National

Drug Resistance Survey for TB, MDR was detected in 2.84% new TB patients and 11.60 % in previously treated patients.³ So in all the studies including ours, MDR-TB was found to occur much more frequently in previously treated patients; however it does occur in new patients as a primary infection.

5. Conclusion

Previous drug treatment is perhaps the most important risk factor for the development of MDR-TB. Now a days, it is also being reported from newly diagnosed TB patients as a primary infection. If not diagnosed and treated early, it may spread rapidly and probably replace the drug sensitive strains. So detection of drug resistance is as important as mere diagnosis of TB and should be done when ever possible. All patients of TB with past history of anti-TB treatment, failure or not responding to treatment, defaulter patients with incomplete treatment should be strongly suspected to have MDR-TB. They should appropriately investigated and treated to limit the spread of MDR strains and improve the patient outcome.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

- Kritski A, Augusto F. Chapter 15: Tuberculosis in Adults. TuberculosisTextbook.com ; 2007,. p. 487–519. Tuberculosis.
- Kumar A, Singh AK, Upadhyay V, Pandey J. Epidemiology of multi-drug-resistant tuberculosis in Northern India. *Biomed Biotechnol Res J*. 2018;2:112–33.
- Revised National tuberculosis Control Program ; 2018,. Annual Status Report.
- World Health Organization ; 2010,.
- Prasad R, Gupta N, Banka A. Multi drug resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management. *Lung India*. 2018;35:78–81.
- Shah NS, Wright A, Drobniewski F. Extreme drug resistance in tuberculosis (XDR-TB): Global survey of supranational reference laboratories for Mycobacterium tuberculosis with resistance to second-line drugs. *Int J Tuberc Lung Dis*. 2005;9:77–77.
- Prasad R, Singh A, Balasubramanian V, Gupta N. Extensively drug-resistant tuberculosis in India: Current evidence on diagnosis & management. *Indian J Med Res*. 2017;145:271–293.
- AS P, M VC, H A, WL C, M R, et al. GeneXpert for TB diagnosis: planned and purposeful implementation. *Glob Health Sci Pract*. 2013;1(1):18–23.
- Pandey P, Pant ND, Rijal KR, Shrestha B, Kattel S, et al. Diagnostic Accuracy of GeneXpert MTB/RIF Assay in Comparison to Conventional Drug Susceptibility Testing Method for the Diagnosis of Multidrug- Resistant Tuberculosis. *PLoS ONE*. 2017;12(1). Available from: [10.1371/journal.pone.0169798](https://doi.org/10.1371/journal.pone.0169798).
- Palomino JC, Martin A. Drug Resistance Mechanisms in Mycobacterium tuberculosis. *Antibiotics*. 2014;3:317–340.
- Blanchard JS. Molecular mechanisms of drug resistance in Mycobacterium tuberculosis. *Annu Rev Biochem*. 1996;65:215–39.
- Telenti A, Imboden P, Marchesi F, Lowrie D, Cole S, et al. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. *Lancet*. 1993;341:647–50.
- LP O. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. *Br Med Bull*. 2005;p. 73–4.
- Bansal SK, Ahir GC, Padda P, Bansal S, Singh B. Prevalence of MDR-TB among new and previously treated patients of pulmonary tuberculosis in DRTB centre of Faridkot - a retrospective study. *Int J Contemp Med Res*. 2017;4(6):1283–1286.
- Girum T, Muktar E, Lentiro K, Wondiyie H, Shewangizaw M. Epidemiology of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the prevalence, determinants and treatment outcome. *Tropical Diseases. Travel Med Vaccin*. 2018;4:1–12.
- Kumar P, Kumar P, Balooni V, Singh S. Genetic mutations associated with rifampicin and isoniazid resistance in MDR-TB patients in North-West India. *Int J Tuberc Lung Dis*. 2015;19:434–443.
- Sethi S, Mewara A, Dhatwalia KS, Singh H, Yadav R, Singh K. TB genotypic diversity in Northern India. *Indian J Med Res*. 2014;139:892–90.

Author biography

Snehal Patil Associate Professor

Prasanna Nakate Associate Professor

Suvarna Patil Medical Director

Yogendra Shelke Assitant Professor

Cite this article: Patil S, Nakate P, Patil S, Shelke Y. Prevalence of multi-drug resistant (MDR) pulmonary tuberculosis in a tertiary care rural hospital in Western Maharashtra, India. *Indian J Microbiol Res* 2019;6(3):237-240.