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Original Article

Prevalence of Pre-extensively Drug-resistant Tuberculosis and Extensively Drug-resistant Tuberculosis among Multidrug-resistant Tuberculosis Patients in South Tamil Nadu

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Abstract

Introduction: Drug resistance in tuberculosis (TB) is a growing global problem. The emergence of extensively drug-resistant TB (XDR-TB) strains is a significant roadblock in successfully implementing TB control programs. This further leads to high morbidity and mortality, especially in immunocompromised patients. The true scale of XDR-TB is unknown. Identification and observation of resistance patterns of XDR-TB strains may help clinicians manage multidrug-resistant TB (MDR-TB) cases.

Aims: This study aims to study the prevalence of pre-XDR and XDR-TB among the MDR-TB strains and clinical risk factors associated with XDR-TB in a tertiary care hospital in South Tamil Nadu.

Materials and Methods: This is a retrospective study conducted in a DR-TB Centre, Tirunelveli Medical College covering four South Tamil Nadu districts. We analyzed around 173 proven MDR-TB cases who were registered and initiated CAT IV regimen in our DR-TB Centre. Baseline second-line drug susceptibility testing for kanamycin and ofloxacin and the follow-up culture of pre-XDR and XDR patients from records were collected from August 2014 to July 2016 analyzed.

Results: Of the 173 patients with MDR-TB, 3 (2%) were XDR MTB strains. Thirty-three MDR-TB isolates (19%) were pre-XDR MTB strains and maximum resistance was observed to ofloxacin 82% (27/33). Socioeconomic status, migration history particularly to Mumbai (25%, *n* = 9), concomitant illness like diabetes mellitus (47%, *n* = 17), and previous intake of 2nd line drugs were significantly associated with the occurrence of XDR-TB.

Conclusions: This study showed the prevalence of XDR-TB compared to the "Global Report on surveillance and Response" which estimated that the prevalence of XDR among MDR-TB patients is 3.2%. MDR-TB cases need urgent and timely drug sensitivity reports for second-line ATT drugs to help the clinicians start proper drug combinations to treat MDR-TB patients and break the transmission chains.

Key words: Extensively drug resistant, Multiple drug resistant, *Mycobacterium tuberculosis*, Second-line drug resistance

INTRODUCTION

The emergence of pre-extensively and extensively drug-resistant tuberculosis (pre-XDR/XDR-TB) is the major hurdle for TB prevention and care programs, especially in developing countries like India. The less emphasis on universal access to laboratory techniques for the rapid diagnosis of TB and drug susceptibility testing (DST) makes the management of multidrug-resistant TB (MDR-TB) a challenge. Early detection of second-line anti-TB drugs resistance is essential to reduce transmission of pre-XDR/XDR-TB strains and adjusting the treatment regimen in MDR-TB.

The emergence of pre-extensively and XDR TB (pre-XDR/XDR-TB) is a significant obstacle for TB prevention in developing countries like India. The less focus on universal access to laboratory techniques for rapid TB diagnosis and DST challenges MDR-TB management. To reduce the transmission of pre-XDR/XDR-TB strains and

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adapt the MDR-TB treatment regime, early identification of second-line anti-TB drug resistance is crucial.[1] MDR-TB is a known phenomenon and is defined as the TB strain resistant to at least two first-line drugs such as rifampicin (RIF) and isoniazid. Pre-XDR TB is the MDR-TB strain that is resistant to either fluoroquinolone (FQ) or second-line injectable drug but not both. The MDR-TB strain that is resistant to any FQs and one of the second-line injectable drugs (capreomycin, kanamycin, or amikacin) is defined as XDR-TB.[2,3] Both XDR and pre-XDR TB are now posing concern on global efforts to control TB.

XDR-TB has been identified in 92 countries across the world according to a WHO report in 2012. India along with Russia and South Africa accounted for 45% of the total MDR-TB and RIF-resistant (RR-TB) cases in 2015 with an estimated 79,000 MDR-TB cases.[4] The exact prevalence of XDR-TB and its extent and magnitude is yet to be identified. Although the global incidence of MDR-TB is increasing, little data are available about the prevalence of XDR and pre-XDR-TB worldwide and in India. In India, the burden of TB is high, but the economic and resource constraints do not allow routine testing to FQ and second-line drug (SLD) resistance.[5] Unnecessary exposure to FQs and injectable aminoglycoside to treat bacterial infections other than TB may contribute to the evolution of resistance to these agents. In countries like India where TB is endemic, the registered practitioners must exercise utmost care while prescribing these drugs to patients in cases other than tuberculosis, keeping in mind the prevalence of drug resistance to these agents.

In 2015, only around 46% of the patients with MDR-TB had achieved treatment success and a 20% death rate was recorded. A poor outcome was reported in 9.5% of patients with XDR-TB.[6,7] Therefore, prevention and control of drug resistance are essential to reduce the death rate and improve treatment outcomes in MDR-TB cases. This study was designed to find out the prevalence of pre-XDR and XDR-TB among the MDR-TB strains and clinical risk factors associated with XDR-TB and create awareness about the community drug sensitivity patterns.

Aim

This study aims to study the prevalence of pre-XDR and XDR-TB among the MDR-TB strains and clinical risk factors associated with them in a tertiary care hospital in South Tamil Nadu.

MATERIALS AND METHODS

This is a retrospective study conducted in a DR-TB Centre, Tirunelveli Medical College covering four South Tamil Nadu districts. We analyzed around 173 proven MDR-TB cases who were registered and initiated CAT IV regimen in our DR-TB Centre. Baseline second-line DST for kanamycin and ofloxacin and the follow-up culture of pre-XDR and XDR patients from records were collected from August 2014 to July 2016 analyzed. The patients were grouped into primary MDR group, category I (XDR-TB) and category 2 (pre-XDR-TB). Sputum samples had been collected according to RNTCP guidelines. The culture was done on LJ medium and the identified *Mycobacterium tuberculosis* complex was subjected to sensitivity testing to SLDs kanamycin and ofloxacin. The patient's demographic data and migration history were obtained from the clinical records.

RESULTS

Of the 173 patients with MDR TB, 3 (2%) were XDR MTB strains. Thirty-three MDR-TB isolates (19%) were pre-XDR MTB strains that are strains are either resistant to ofloxacin (OFX 82%) or kanamycin (KM 18%). We observed maximum resistance to ofloxacin 82% (27/33). This may probably be due to the random use of quinolones by many registered and non-registered practitioners for common diseases. This highlights the problem in opting drug regimen to treat MDR cases. More than half (78%, n = 28) of these patients had a history of previous TB treatment. Nearly 22% of patients (n = 8) were primary MDR-TB. Among XDR-TB, all of them had a previous anti-TB therapy, with 67% of patients found to be diabetic, whereas in pre-XDR-TB, 42% of patients had diabetes. Socioeconomic status, migration history particularly to Mumbai (25%, n = 9), concomitant illness like diabetes mellitus (47%, n = 17), and previous intake of 2nd line drugs were significantly associated with the occurrence of XDR-TB. Only one of the patients enrolled was HIV seropositive (2.8%). HIV infection is not more common among drug-resistant TB patients than in the general population. Figure 1 depicts the analysis of pre-XDR and XDR-TB cases.

DISCUSSION

Early identification of SLD resistance plays a key role in TB control and management and also to optimize the treatment regimen composition. SLD resistance can impose a major economic burden in developing countries due to resource constraints and implications on short treatment regimens, new therapeutic agents, and new rapid diagnostic tools.[8] In the present study, 173 patients with MDR-TB were analyzed and the presence of pre-XDR and XDR TB strains was found in 19% and 2%, respectively, Figure 2. The percentage of pre-XDRTB was higher than XDR

strains and two SLDs OFX and KM were tested in our study. In Poland, the prevalence of pre-XDR-TB among MDR-TB patients is 12.1%, and in China, it is 31%.[9,10] The exact prevalence of pre-XDR and XDR-TB in India is not available and a few Indian studies report a prevalence rate of 2.4–33.3%.

Among the 33 pre-XDR-TB isolates, 27(82%) were resistant to OFX and 6 (18%) were resistant to kanamycin, Figure 3. This finding is similar to the study findings of Singhal *et al.* who also reported a higher resistance to OFX by the pre-XDR-TB isolates. The percentage of resistance in his study was 39% which is higher than the other studies ranging from 7.7% to 27.6%.[11] The increased resistance to ofloxacin highlights the problem in forming drug regimen to treat MDR cases. Similarly, the resistance to kanamycin in his study was 1.1%, and in our study, it is 18%. Various other studies report a prevalence rate ranging from 0.6% to 14.6%.[12] Myneedu *et al.* associates in their study showed 20.17% XDR-TB strains among a total of 223 MDR-TB strains. Global studies show a prevalence of 6.5% XDR stains in the USA, 10.3% in Germany, and 14.3% in Italy. In a 2010 WHO report, 58 countries reported the presence of XDR-TB strains among MDR-TB patients.[13] Apart from quinolones, kanamycin resistance pattern is a common finding ranging from 20% to 60% resistance documented in CDC and was seen in this study also (18%).[14]

In our study, 22% of the cases were primary MDR-TB cases and majority (78%) were previously treated for TB. This finding might indicate a significant public health threat given that there could be a progressive drug-resistant strain transmission in the population. Another interesting feature observed in our study was the migration history, especially to Mumbai where it showed 25% occurrence of XDR-TB, Figure 4. Concomitant illness like diabetes and previous intake of 2nd line drugs were also observed to be significantly associated with XDR-TB occurrence in this study, Figure 5. This may be due to the widespread and unchecked use of second-line anti-tuberculous drugs for other diseases like URTI and for urinary tract infections. Shah *et al.* in his study found that 70% of the total XDR-TB strains were resistant to SLD.[15] Studies also indicate that overcrowded/slum areas and high temperature and low altitude areas are at high risk of TB transmission and subsequent development of resistant strains.

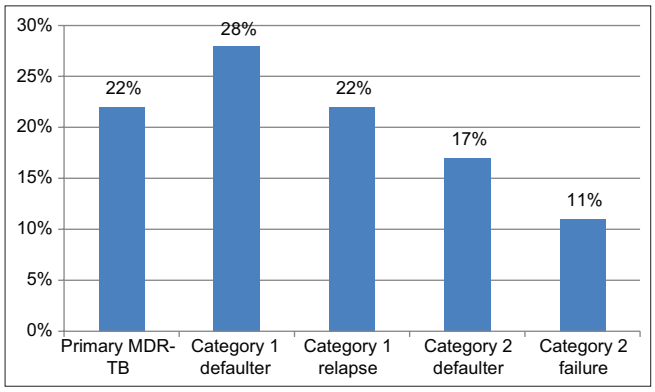

Figure 1: Analysis of pre-extensively drug-resistant (XDR) and XDR tuberculosis

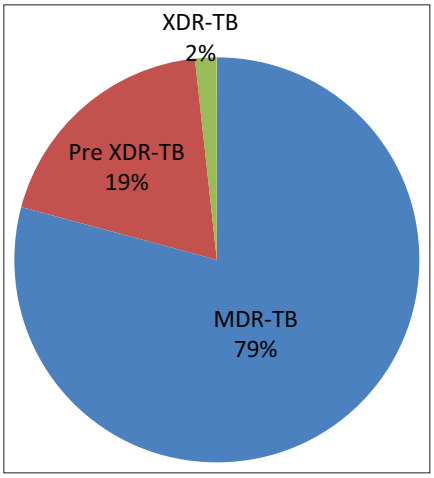

Figure 2: Pattern of drug resistance

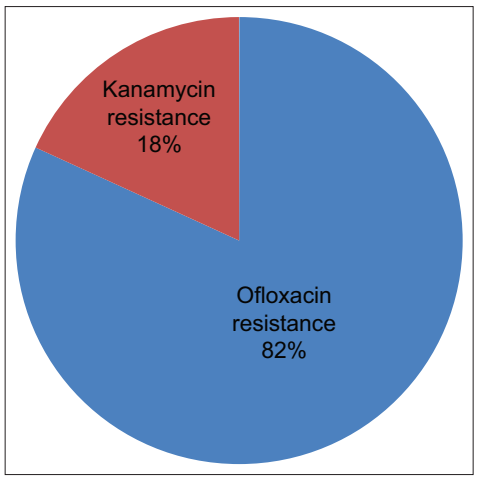

Figure 3: Percentage of resistance to second-line drug among pre-extensively drug-resistant tuberculosis

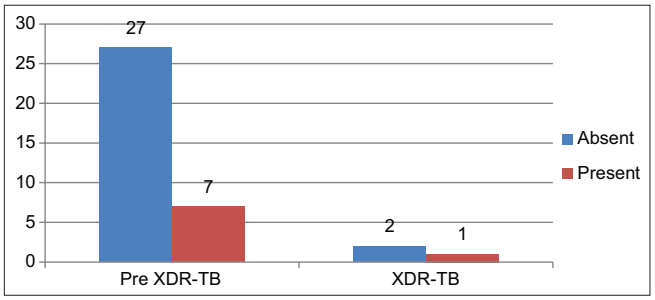

Figure 4: History of Mumbai residence

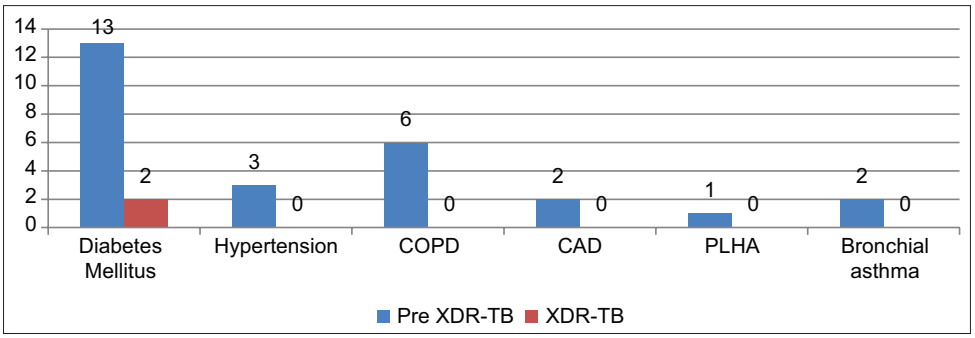

Figure 5: Comorbidities in pre-extensively drug-resistant (XDR) and XDR tuberculosis

Although our study showed a low prevalence of XDR-TB strains, the magnitude and distribution could not be estimated from the available data. Early diagnosis of resistance, appropriate therapy, and improved patient awareness for TB treatment play a crucial role in the control of MDR-TB and in interrupting the transmission chains. Future efforts should focus on strengthening of infrastructure for early diagnosis and treatment of MDR-TB and utilization of DOTS and DOTS plus strategy to increase community awareness, which can greatly avoid SLD resistance.

CONCLUSIONS

This study showed the prevalence of XDR-TB compared to the "Global Report on surveillance and Response" which estimated that the prevalence of XDR among MDR-TB patients is 3.2%. MDR-TB cases need urgent and timely drug sensitivity reports for second-line ATT drugs to help the clinicians start proper drug combinations to treat MDR-TB patients and break the transmission chains.

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