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Original Research Article

Prevalence of Drug Resistance in *Mycobacterium Tuberculosis* in Western Rajasthan among Paediatric Patients

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Conflict of interest: Nil

Abstract:

Background: Drug resistance tuberculosis is a significant clinical disease that can lead to poor results in tuberculosis patients. Drug resistance in *Mycobacterium* TB is most common in first-line anti-tubercular medicines, primarily rifampicin and isoniazid. Multidrug-resistant tuberculosis and broad drug resistance tuberculosis hinder our efforts to eradicate TB.

Methods: Present study was a cross-sectional study. Samples from patients belonging to one year to 15 years age group, received from different districts of Western Rajasthan, were received and tested for drug resistance by CBNAAT and Line probe assay for drug resistance.

Results: Out of 200 TB-positive cases, 61% were females and 39% were males. The mean age of study population was 13.05 (±3.15) years.

Conclusion: The high prevalence of drug resistance among TB patients in our study was noted. Furthermore, Jalore district was found to have 9.5% cases of XDR-TB, which is alarming.

Keywords: Line probe assay; First line-LPA; Second line-LPA; CBNAAT; MGIT; MDR-TB; XDR-TB.

Introduction

Tuberculosis (TB) is an air-born, communicable disease caused by *Mycobacterium tuberculosis*. It is on the top of the list of the leading causes of death by single infectious agents. It is worldwide prevalent with the capability of infecting any part of the body. Approximately 10 million people are infected every year globally and 1.5 million people die from TB each year. [1]

TB is curable and preventable however, lack of awareness and adherence to treatment is causing higher treatment failure rates and the spread of drug resistance in *Mycobacterium tuberculosis*. It has been reported worldwide irrespective of the economic status of the country. Drug resistance in tuberculosis is a serious clinical condition that might lead to poor outcomes. First-line treatment drugs include rifampicin, isoniazid, pyrazinamide and ethambutol which are very effective in the treatment and prevention of disease. The most prevalent drug resistance in *Mycobacterium tuberculosis* is seen in rifampicin and isoniazid. Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis resistant to at least two first-line drugs isoniazid (INH) and rifampicin (RIF). MDR-TB remains a clear threat and an obstacle to eradicating tuberculosis.

Additional resistance in the life-saving second-line drugs has been reported worldwide in MDR strains and leading to pre-XDR strains or XDR strains. Patients with MDR-TB roughly account for 4.1% of all new and 19% of retreatment TB cases globally, although wide regional and country differences occur. [2] The global incidence of Fluoroquinolones resistance among MDR-TB cases were 21% according to WHO 2019 TB report. [3]

It is crucial to recognize the drug resistance at the earliest stage before its resistance progresses to the next category and leaves no choice for treatment but unfortunately, to date limited data are available on the prevalence of Pre-XDR-TB worldwide, including in India. The aim of the present study was to determine the prevalence and resistance pattern

of among *Mycobacterium tuberculosis* isolates in Western Rajasthan.

Material and Methods

Study design and participants: A cross-sectional study was carried out in TBC & DST laboratory of Kamala Nehru Chest Hospital, Jodhpur which included nine districts of Western Rajasthan. Two sputum specimens (spot and morning) were collected in 50 mL wide-mouthed sterile falcon tubes from 200 participants from 1 year to 15 year age group. All types of specimens were collected irrespective of disease site involved. Demographic data like age, gender, residence, socioeconomic status were also collected. For diagnosis of tuberculosis microscopy, CBNAAT and liquid culture (MGIT 960) were performed and for drug resistance detection Line probe assay (first-line and second-line drugs) was performed. [4] Data were analysed using SPSS 24 software.

Exclusion Criteria: Repeat specimen, close contact of tuberculosis-positive patient, patient with a history of previous tuberculosis treatment, Non-tuberculous Mycobacteria (NTM), or incomplete demographic data were excluded from this study. Each sample was examined microscopically for the presence of *Mycobacterium tuberculosis* using Ziehl-Neelsen (ZN) staining. All smear-positive specimens were directly processed for LPA (Genotype MTBDR plus V 2.0 assay and Genotype MTBDRsl Ver 2.0 assay) directly from the processed specimen according to manufacturer's instructions. In the case of smear-negative specimen, a subsequent liquid culture was performed by the N-acetyl-L cysteine sodium hydroxide method. Culture-positive specimens were subjected to immune-chromatographic assay for detection of the MPT-64 antigen. MPT64 positive specimens were *Mycobacterium tuberculosis* complex and were further subjected to LPA (First line and second line). [5–8]

Result

Out of 200 TB-positive cases, most of the respondents were female 122 (61%) followed by male 78 (39%) with a mean age of 13.05 years. The range varied from 1 year to 15 years with mean age of our study population is 13.05 years (SD±3.15). 153 (76.5%) specimens were sensitive to both rifampicin and isoniazid in the first-line- Line probe assay. 41 (20.5%) specimens were found to be resistance to Rifampicin, Isoniazid or Rifampicin and Isoniazid both. These resistant strains were further tested for any additional resistance to second-line drugs (FQ & SLID) by LPA. Among drug resistance strains, 5 (2.5%) strains were MDR strain, 5 (2.5%) Pre-XDR and 2 (1%) XDR strains. [Figure 1]

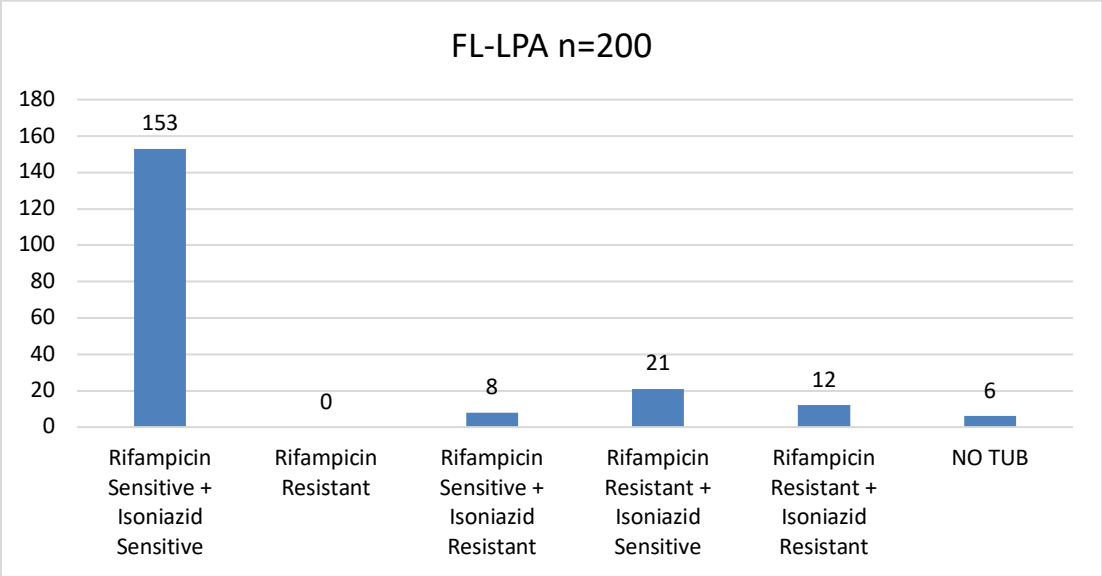

Figure 1: Drug resistance pattern of *Mycobacterium tuberculosis* strains by FL-LPA

However, 6 strains did not develop TUB band in FL-LPA which were excluded form Second Line LPA analysis. Drug resistance status by FL-LPA technique showed the majority of specimens, 153 (76.5%), to be sensitive to both rifampicin and isoniazid; 12 (6%) were rifampicin isoniazid-resistant; 21 (10.5%) were rifampicin mono-resistant; and 8 (4%) were isoniazid mono-resistant. All enrolled cases from Barmer district were rifampicin and isoniazid-sensitive. The highest resistance to both rifampicin and isoniazid was observed in Jalore (9.5%), followed by Bikaner in 9% of cases. All the specimens from Ajmer were rifampicin mono-resistant, followed by Jalore district, in which 6 (28.5%) cases were found to be rifampicin mono-resistant. However, isoniazid mono-resistance is seen highest in the Sirohi district in 3 (21.4%) cases. [Table 1]

Table 1: Drug resistance of *Mycobacterium tuberculosis* strains to first line drugs

District	RIF, INH Sensitive	RIF, INH Resistance	RIF Mono - Resistance	INH Mono-Resistance	No TUB
Ajmer (1)	0	0	1(100)	0	0
Barmer (2)	2(100)	0	0	0	0
Bikaner (11)	8(72.7)	1(9)	2(18)	0	0
Hanumangarh (24)	19(79)	2(8.3)	1(4.1)	0	2(8.3)
Jaisalmer (2)	1(50)	0	1(50)	0	0
Jalore (21)	12(57.1)	2(9.5)	6(28.5)	1(4.7)	0
Jodhpur (75)	61(81.3)	4(5.33)	6(8)	3(4)	1(1.3)
Pali (37)	30(81)	2(5.4)	1(2.7)	1(2.7)	3(8.1)
Sri Ganganagar (13)	11(84.6)	0	2(15.3)	0	0
Sirohi (14)	9(64.2)	1(7.1)	1(7.1)	3(21.4)	0
Total (200)	153	12	21	8	6

RIF- Rifampicin, INH- Isoniazid

Table 2: Drug resistance categories of Tuberculosis patients

Districts	MDR Cases n=5(%)	Pre-XDR n=5(%)	XDR Cases n=2(%)
Ajmer (1)	0	0	0
Barmer (2)	0	0	0
Bikaner (11)	1(9)	0	0
Hanumangarh (24)	2(8.3)	0	0
Jaisalmer (2)	0	0	0
Jalore (21)	0	0	2(9.5)
Jodhpur (75)	01(1.3)	3(4)	0
Pali (37)	0	2(5.7)	0
Sri Ganganagar (13)	0	0	0
Sirohi (14)	1(7.1)	0	0
Total (200)	5(2.5)	5(2.5)	2(0.1)

Findings from SL-LPA showed 5 (2.5%) cases in each category MDR and Pre-XDR. 2 cases of MDR category were recovered from Hanumangarh followed by Bikaner, KNCH and Sirohi each with one case. Only 2 (1%) were confirmed as XDR cases and these both strains were recovered from patients belonging from Jalore district. [Table 2]

Discussion

Study enrolled 200 participants with mean age of 13.05 years (SD±3.15). S. R. Mazta et al., and Malik AA et al., carried out studies where mean age of the children was similar to our study with value of 12 years and 16 years respectively. [9,10] However, Sanjay K. Jain et al., (2013), reported mean age in their study was 31 months. [11] The variation in age group maybe due to the definition of children followed by authors. We recorded higher number of female patients 122 (61%).

Similar findings were recorded by S. R. Mazta et al., with 64.5% and Hesseling AC et al., 62.6% cases. [9,12] In contrast, study conducted by Loh SW et al., and Tao NN et al., reported higher number of male participants in their study 52%, and 56.5% respectively. [13,14] Reason behind these findings may be cultural practices and geography distribution. Higher outdoor activity (farming), cultural practices (social gathering) sharing closed space may increase chances of TB spread which might be the reason of high number of female cases in our study population.

Resistance to first line drugs (Rifampicin and Isoniazid) was observed in 20.5% cases in our study. This percentage is in line with the findings of Tao NN et al. where drug resistant cases were 18.9%. [14] Opposite to our findings, Song WM et al., reported less drug resistance cases with 13.59% of the total cases. [15] This variation in drug resistance may be due to the well-established treatment guidelines, adherence of patient to treatment, better diagnostic facilities which can improve treatment outcome. 2.5% of cases in our study were MDR and Pre-XDR, which is very less than the findings reported by WHO with 3.6% of MDR and 20% cases of Pre-XDR worldwide. We also report 1% cases of XDR cases in our study which is very less in number and a positive finding in compression to available literature where XDR prevalence varies from 6.2% to up to 9.7%. This high-level resistance to second line drugs may be due to easy access to the second line drugs in India, over prescription of antibiotics, over the counter availability of the drugs and incomplete treatment or non-adherence of patients to treatment. This high-level drug resistance can be controlled by early diagnosis and monitoring the treatment at regular intervals.

Our study contributes to the literature by reporting the drug resistance findings. These findings can help to monitor the drug resistance spread, monitor the treatment and formulating guidelines.

Conclusion

The high proportion of drug resistance among TB patients in our study is alarming in the region. Further study is warranted to explore the role of various factors (demographic or ecological) on the observed high distribution of DR-TB, treatment outcome and identify transmission network in the community to locate hotspots for targeted interventions.

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