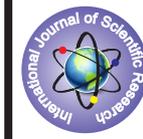


Geographical Distribution and Resistance pattern of Multidrug Resistant Pulmonary Tuberculosis Patients in Western Rajasthan



Medicine

KEYWORDS: DR TB (Drug Resistant Tuberculosis), INH (Isoniazide), LPA (Line Probe Assay),

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ABSTRACT

Multidrug resistant tuberculosis (MDR-TB) is caused by Infection with *Mycobacterium tuberculosis* which is resistant to both isoniazid (INH) and rifampicin (RIF), with or without any other anti tubercular drug. To find out the number of MDR-TB diagnosed cases who were successfully initiated the treatment in MDR TB Centre of western Rajasthan also, to determine the geographical distribution of MDR TB in western Rajasthan and to facilitate early diagnosis and treatment. This five year observational, retrospective, hospital base, study was carried out in tertiary center of western Rajasthan, Kamla Nehru chest hospital, Dr. S.N. medical college Jodhpur Rajasthan, India. During the period of March 2012 to December 2016, 1225 cases of multidrug resistant tuberculosis, from 6 districts of western Rajasthan around Jodhpur were admitted and successful initiation of category 4. These patients were subjected to drug sensitivity test by a molecular diagnostic method, Using Genotype MTBDR plus kit. Out of 1225 cases of MDR TB, majority of 426/1225 cases were from Jodhpur district, 22.5% were from Pali district, 12.97% from Jalore, 11.26% from Barmer district and 5.63% from Jaisalmer district. Among these 1225 cases, Drug resistance confirmed by LPA in 864(70.5%) and gene Xpert base in 361(29.5%). 207/1225 cases were rifampicin mono resistance and 657/1225(53.6%) were both isoniazid and rifampicin resistant based on LPA. Male female ratio was 3:1. The Geographical distribution of Multi drug resistant pulmonary tuberculosis in western Rajasthan is unequal as 1/3rd cases of total from Jodhpur district only. It needs early diagnosis by molecular diagnostic method and prompt treatment in other part of western Rajasthan to reduce the spread of MDR TB cases.

Introduction:

Tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, has affected mankind for over 5000 years, and still continues to be a leading cause of morbidity and mortality.¹

TB is the first infectious disease declared by the World Health Organization (WHO) as global health emergency.² Multidrug resistant tuberculosis (MDR-TB) is caused by infection due to *Mycobacterium tuberculosis* resistant to Isoniazid and Rifampicin, with or without resistance to other antitubercular drugs.³

In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide. Globally, an estimated 3.3% of new patients and 20% of previously treated patients have MDR-TB.⁴ There are an estimated half million (480,000) new cases of multi drug resistance tuberculosis around the world every year. TB creates more orphans than any other infectious disease.⁴

MDR-TB results from infection with already drug-resistant bacilli or may develop during a patient's treatment, mostly due to administration of improper regimens in chemotherapy of drug-susceptible TB patients and failure to ensure patient compliance. Laboratory facilities for drug susceptibility testing are inadequate, thus diagnosis is often missed, and the actual number of global drug resistant tuberculosis cases remains unestimated.⁵ The cause of drug resistant tuberculosis is loss of Sensitivity to drugs due to genetic mutation.⁶

In Western Rajasthan, MDR-TB patients are frequently admitted at the kamla Nehru chest hospital, of Dr. S.N. medical college, Jodhpur, Rajasthan for initiation of category 4. This study presents our five year experience with MDR-TB patients in terms of socio demographic profile, drug susceptibility patterns, and geographical distribution.

Material and methods:

This is five years retrospective, hospital data based, observational study (March 2012-December 2016) was carried out in tertiary care center of western Rajasthan, Kamla Nehru chest hospital, Dr. S.N. medical college, Jodhpur, Rajasthan. Approval was received from ethical committee of Dr. S.N. medical college ethical committee. Informed consent was taken. To determine the drug resistance pattern and geographic distribution of MDR TB cases in western

Rajasthan admitted in kamla Nehru chest hospital, Jodhpur, to facilitate early diagnosis and treatment. Also to find out the number of those diagnosed cases who were successfully initiated the treatment in MDR TB Centre of western Rajasthan.

Data was entered using Microsoft Excel 2007 and analyzed using Software SPSS 24th Version. Statistical analysis was done by using Chi square test and P Value <0.05 as significant.

Inclusion Criteria

1. Rifampicin mono-resistant cases confirmed by molecular DST (Line Probe Assay).
2. All multidrug (isoniazid and rifampicin) resistant tuberculosis cases.
3. All rifampicin resistant (gene expert based) retreatment case.

Exclusion criterias

1. Extra pulmonary MDR-TB cases
2. Resistant Tuberculosis other than Multi drug resistant tuberculosis
3. Transferred in patients

Total 1225 MDR-TB cases were admitted in tertiary care center, Jodhpur for initiation of category 4, according to the above criteria. These MDR-TB patients were from of six different districts of western Rajasthan Jodhpur, Pali, Sirohi, Jalore, Barmer and Jaisalmer. All sputum microscopy positive samples were subjected to Line Probe Assay (LPA) by Genotype MTBDR plus kit, where as microscopy negative samples were subjected to culture by LJ media. Culture was observed for 8 weeks and weekly reading was done. If culture became positive then they were subjected to LPA to know their drug sensitivity by Genotype MTBDR plus kit. Then resistance to INH or Rifampicin or both could be determined by comparing the strip given along with the diagnostic kit.

The whole procedure was divided into three parts: 1) DNA extraction; 2) PCR amplification and; 3) Hybridization. We have used MTBDR plus kit for the present study and followed the instructions given by the manufacturer of the kit while performing each of the above mentioned procedures.⁷

Finally cases with drug resistance to Rifampicin or INH or resistance

both were identified. Then patients were sent from different district level to tertiary care center for pretreatment evolution and initiation of category 4 treatment in MDR TB Ward, under supervision of senior medical officer under kamla Nehru chest hospital, Dr S.N. medical college, Jodhpur, Rajasthan.

Results:

In present study, 1225 MDR-TB cases were admitted in our center from six districts of western Rajasthan, including Jodhpur district, over five years march 2012 to December 2016. Age of the patients was ranging from 9 to 75 years and male-female ratio was 4:1. Study population consists of predominantly male 78.6% (963/1225), most of them 73.83% in the age group of 20-49 years. Female in the group 262/1225(21.4%) are mostly in the age group of 20-29 years (77/262) (Table no. 1).

Majority (73.8%) of male patients were in the economically productive age group. The male to female ratio was 963/262. Mean age of females (31.86 ±12.50 years) was less than that of males (37.56±12.84). This difference was found to be statistically significant ($t=-3.202$, $p=0.007$) whereas the mean age of our study was 36.33 years. Majority (73.7%) of patients belongs to economically productive age group (20-50 years), standard deviation (SD) 13.05 years; range 14 – 85 years).

This study found that maximum number of MDR-TB cases 426/1225(34.77%) were from Jodhpur district and 22.85%, 12.97%, 11.26% and 5.63% cases were from Pali, Jalore, Barmer and Jaisalmer respectively (Table no. 2). Out of 1225 MDR-TB cases, maximum number MDR-TB cases 302 (24.65%) were received in the 2014. 947/1225 (77.3%) of our study patients belonged to rural backgrounds.

207/1225(16.9%) patients were rifampicin mono-resistant and 657/1225(53.6%) patients were both isoniazid and rifampicin resistant based on LPA. 361/1225(29.5%) patients on retreatment group were put on treatment on the basis of gene expert. (Table no. 3)

TABLE-1
Age and gender distribution among study patients

Age	Male		female		total	
	Number	%	number	%	number	%
<19	65	6.79	17	6.34	82	6.69
20-29	288	29.46	77	30.67	365	29.79
30-39	216	22.56	70	26.11	286	23.34
40-49	207	21.63	45	16.79	252	20.57
>50	187	19.54	53	19.77	240	19.59
total	963 (78.63%)	100	262 (21.4%)	100	1225	100

TABLE-2
Geographical distribution among study patients

District	No. of Patients	Percentages
Barmer	138	11.26%
Jaisalmer	69	5.63%
Jalore	159	12.97%
Jodhpur	426	34.77%
Pali	280	22.85%
Sirohi	150	12.25%
Total	1225	100%

TABLE-3
Distribution of patients according to methods of diagnosis and Resistance pattern

Resistance pattern	Number (%)
Rifampicin mono-resistant (LPA)	207(16.9)
Multi-drug resistant (LPA)	657(53.6)
Rifampicin resistant retreatment (Gene expert based)	361(29.50)
Total	1225(100)

Discussion:

MDR TB has become a growing concern and a posing threat to the control of TB along with the additional scourge of HIV. Total 480000 incident cases of MDR-TB were estimated worldwide in 2016 among notified pulmonary TB patients. The global incidence of primary and secondary resistance was 3.6% and 21% respectively.²

Almost 50% of MDR TB cases worldwide are estimated to occur in China and India.² The incidence of primary and secondary resistance in India was 2.2% and 11-19% respectively.³

Out of the 1225 study participants, 963/1225(78.6%) patients were male, 262 (21.4%) patients were female and mean age was about 36.33 years. Similar finding was found in other studies⁽⁹⁻¹⁴⁾ (30.32-37.08 years). Dr Nirmalya Manna et al⁹ from Kolkata in 2014 found that 70.7% were male and 29.2% female, Sunita Tripathy et al¹⁴ from north Bihar in 2013 found that 79.4% were male patients and 20.6% were female.

Of the study subjects, 903/1225(73.7%) were between 20-49 years old, as shown in Table 1. Age distribution of the study population indicates the dominance of productive age group (20 - 49 years), the finding being similar to other studies.⁽⁹⁻¹⁴⁾ Dr Nirmalya Manna et al⁹ from Kolkata found that 75.2% were productive age group (20 - 49 years).

Our study found that majority of patients were from rural area 947/1225(77.3%) with only 278/1225(22.7%) patients being from urban area. Sunita Tripathy et al¹⁴ from north Bihar showed 71.4% rural and 28.6% urban population. Gneyaa bhatt et al¹⁰ from Ahmadabad in 2012 showed 58.0% rural and 42% from urban area. Our result showed higher value than other studies because as per census report of India 2011 rural population is higher in Rajasthan than in other part of India.¹⁵

864/1225(70.5%) patients were LPA based diagnosed and 361/1225(29.5%) patients were put on treatment on the basis of gene expert. 207/1225(16.9%) patients were rifampicin mono-resistant and 657/1225(53.6%) patients were both isoniazid and rifampicin resistant based on LPA. These findings were similar to Dr Nirmalya Manna et al¹¹ a study in Kolkata, where among total 53.7% patients were found to be resistant to Rifampicin only and 46.3% to both Rifampicin and Isoniazid. Sunita Tripathy et al¹⁴ study in north Bihar showed 65.4% LPA and 25.6% CBNAAT based diagnosis. In Dr Nirmalya Manna et al¹¹ study showed 65.8% LPA based and 24.7% CBNAAT based and Sarala Menon et al¹² study in Mumbai showed 74.4% LPA based and 25.6% patients were put on treatment on the basis of gene expert.

This study found that maximum number of MDR-TB cases 426/1225(34.77%) were from Jodhpur district (Table no. 2), where early diagnostic facility are available and much less cases, i.e., 12.97%, 11.26% and 5.63% cases were from Jalore, Barmer and Jaisalmer respectively. The reason behind this may be, because of availability of molecular diagnostic method are situated in Jodhpur, which are within the reach of the patients. Therefore, there are needs for rapid diagnosis by molecular method in other regions of western Rajasthan also, to facilitate early treatment and to prevent the spread of multi drug resistant pulmonary tuberculosis.

Previously LPA and CBNAAT sample were sent to Ajmer for their drug resistance testing, but now LPA machine is established in Dr. S.N. Medical College. Therefore all the cases of multidrug resistant TB are diagnosed and treated here. Since CBNAAT is available in all the districts of western part of Rajasthan so that number of cases will probably increase in future.

Conclusion:

Health education regarding spread of disease, early detection of MDR-TB by strengthened laboratory support, effective therapy, implicating innovative control measures, would interrupt the

ongoing transmission and control this emerging epidemic. All cases of diagnosed MDR TB cases were initiated treatment in Kamla Nehru Chest hospital, Dr. S.N. medical college, Jodhpur. It is high time to establish modern laboratories with molecular diagnostic facility in each district to diagnose MDR TB in early stage to prevent spread of MDRTB.

References:

1. Sarala Menon, Sujata Dharmshale, Chhaya Chande, Aruna Gohil, Sunil Lilani, Salim Mohammad, et al. Drug resistance profiles of Mycobacterium tuberculosis isolates to first line anti-tuberculous drugs: A five years study. *Lung India* 2012; 29(3): 227-31.
2. WHO Global Tuberculosis Report 2016. Management of Tuberculosis Training for Health Facility Staff WHO/CDS/TB/2003.314a.
3. Sharma SK, Mohan A. Multidrug-resistant tuberculosis. *Indian J Med Res.* 2004;120:354-76.
4. World Health Organization. Global tuberculosis report, 2015. WHO/HTM/TB/2015.08. Geneva, Switzerland: WHO, 2015.
5. Zumla A, Abubakar I, Raviglione M, Hoelscher M, Ditiu L, McHugh TD, et al. Drug-resistant tuberculosis—current dilemmas, unanswered questions, challenges and priority needs. *J Infect Dis.* 2012; 205(suppl 2):S228-40. Epub 2012 Apr 3.
6. David HL. Probability distribution of drug-resistant mutants in unselected [7] populations of Mycobacterium tuberculosis. *Appl Microbiol.* 1970; 20:810-14.
7. HAIN Lifescience GmbH. Rapid diagnosis of tuberculosis, mycobacteriosis and Leprosy. www.hain-lifescience.de
8. TB India 2016; Revised National Tuberculosis Control Programme; ANNUAL STATUS REPORT; Introduction: P 12.
9. Dr Nirmalya Manna et al Kolkata, India Drug resistance pattern, related socio-demographic factors and preventive practices among MDR-TB patients: An experience from a tertiary care setting (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861. Volume 13, Issue 9 Ver. VI (Sep. 2014), PP 16-21 www.iosrjournals.org
10. Gnenya bhatt et al an epidemiological study of multi drug resistant tuberculosis cases registered under rntcp of ahmedabad city. *Indian j tuberc* 2012; 59: 18-27
11. Julia V. Ershova et al in 2012 Epidemiology of Primary Multidrug-Resistant Tuberculosis, Vladimir Region, Russia *Emerging Infectious Diseases* • www.cdc.gov/eid • Vol. 21, No. 11, November 2015
12. Sarala Menon et al Drug resistance profiles of Mycobacterium tuberculosis isolates to first line anti tuberculous drugs: A five years study *Lung India* • Vol 29 • Issue 3 • Jul - Sep 2012
13. Poulomi Mukherjee et al R. G. Kar Medical College, Kolkata Sociodemographic and clinical profile of multi drug resistant tuberculosis patients: a study at drug resistant tuberculosis centers of Kolkata (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279 0861. Volume 14, Issue 8 Ver. IV (Aug. 2015), PP 52-58 www.iosrjournals.org
14. Sunita Tripathy et al Prevalence of Multidrug Resistant Pulmonary Tuberculosis in North Bihar *Journal of Clinical and Diagnostic Research.* 2015 Nov, Vol-9(11): LC09-LC12
15. india census 2011 © 2010-11 - The Registrar General & Census Commissioner, India, New Delhi-11001.