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Multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* strains in geriatrics: An analysis and its implications in tuberculosis control

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ABSTRACT

Objective: This study aimed to analyze the trends of tuberculosis (TB) disease, drugs susceptibility patterns in geriatric TB over a period of three years (from 2010 to 2012).
Materials & methods: In this study, laboratory data on diagnosis of geriatric tuberculosis suspected patients (age ≥60 years) was analyzed retrospectively at National Reference Laboratory (NRL).
Results: Among 12,140 geriatric TB suspects, 1621 (13%) were acid-fast bacillus (AFB) smear-positive and 10,519 (87%) were smear-negative. Analysis of 915 culture results showed 470 (51%) as positive for *Mycobacterium tuberculosis* complex (MTBC), 63 (7%) contaminated and 36 (4%) identified as mycobacteria other than tuberculosis (MOTT). A total 210/470 (45%) were multidrug-resistant TB (MDR-TB) strains. Among the mono-resistant strains, isoniazid mono-resistant was found more frequently (134/470, 28%) whereas, it was least among rifampicin mono-resistant 5/470 (1%). The second-line drug susceptibility testing (DST) results showed 7% (17/240) extensively drug-resistant TB (XDR-TB) strains. Most common second line mono-resistant strain was observed with ofloxacin, 16% (38/240).
Conclusion: This study shows high number of MDR/XDR geriatric TB patients at tertiary care TB hospital. The study highlighted the need of separate line of early identification, diagnosis and treatment of geriatric TB patients. However, further study with improved sample size may needed to confirm the findings.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), represents a significant disease burden over the world [1–4]. TB is known for its predilection among young people, however it is emerging as a significant health problem in the geriatric/elderly also i.e. aged 60 years or above [5,6]. Its symptoms among geriatric people are often non-specific, usually construed as changes related to ageing [7–9]. This often leads to delayed diagnosis and more advanced stage of disease at presentation [10]. In developed countries though, the disease has shown an overall declining trend, the cases of infection are on the rise amongst geriatrics [11–13]. During 1953 in USA, 13.8% of the newly reported TB cases belonged to patient aged 65 years and above. By 1979, it had doubled to 28.6%, despite the fact that the general geriatric population had only increased by 3%. The geriatric were the single largest group of patients with active TB by the late 1980s, with an increase in fatalities among them [14].

High prevalence of drug resistant TB, its management is a major challenge in India and other developing countries [15,16]. Increase in mortality and incomplete treatment of TB among geriatric TB, together add to the aftermath of disease [17,18]. In India, handfuls of studies have been undertaken on TB related problems amongst the geriatric people, and data on drug susceptibility testing (DST) against *Mtb* strain is hardly available. On the other hand, with increasing population of geriatrics, incidence of TB is also rising. The problem of geriatric TB is not getting the attention it needs. The study aimed to identify the frequency of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) among geriatric suspected TB patients by analyzing 3 years laboratory data.

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2. Materials and methods

2.1. Study design

This retrospective study was undertaken at the National Reference Laboratory (NRL), Department of Microbiology, National Institute of Tuberculosis & Respiratory Diseases (NITRD), New Delhi, India. The laboratory catering one million populations and provides mycobacterial culture and DST facilities to 8 states of north eastern India and own institute/hospital (NITRD, New Delhi). Laboratory data of mycobacterial investigations of ≥60 years old patients from January 2010 to December 2012 were retrieved from laboratory records and analyzed.

For sample receiving, the laboratory followed the revised national tuberculosis control programme [RNTCP, now called National Tuberculosis Elimination Programme (NTEP)] guidelines. As a result, if samples were found to be improperly labeled, or to have broken/leaked container, they were rejected, and a fresh sample was requested. All samples received in the laboratory were initially subjected to acid-fast bacillus (AFB) smear examination followed by mycobacterial culture, as per printed requisition form filled by the clinician. The DST was performed (as per requisition) when mycobacterial culture revealed *Mtb* positive results.

2.2. Acid-fast bacillus (AFB) smear examination

For the samples requiring smear examination, Ziehl-Neelsen (ZN) acid-fast staining was used to demonstrate the *Mtb* as per standard procedure [19].

2.3. Decontamination

Samples referred for culture were subjected to decontamination by using N-acetyl-L-Cysteine sodium hydroxide (NALC-NaOH) method where final concentration of NaOH was 1% [20]. In the final step, sputum sediment was mixed with 1–1.5 μl phosphate buffer (pH 6.8) and further used for inoculating solid or liquid medium for mycobacterial culture.

2.4. Mycobacterial culture

Culture was performed using solid or liquid media as per information given in culture performa duly filled by attending physician. For solid culture, Lowenstein-Jensen (L-J) medium was inoculated with a loopful of decontaminated samples; and incubated for 8 weeks at 37℃ (20). The reading for mycobacterial growth was taken on every week and the results were entered in culture register. The positive cultures were identified as *Mtb* complex (MTBC) by routine biochemical tests such as niacin, nitrate and heat resistant catalase tests [21]. For liquid culture method, 500 μl decontaminated sputum samples were inoculated in middle-brook 7H9 media and incubated in mycobacterium growth indicator tube (MGIT)-960 instrument [20]. The instrument reads the tubes every hour for increased fluorescence. The fluorescence is analyzed by instrument to determine if the tube is positive. The Instruments culture positive tubes were subjected to ZN smear microscopy and lateral flow assay to confirm as having MTBC.

The identified cultures were subjected to DST for first line anti-tuberculosis drugs such as. isoniazid (0.1 μg/ml), rifampicin (1 μg/ml), ethambutol (5 μg/ml) and second line anti-tuberculosis drugs, such as kanamycin (2.5 μg/ml), capreomycin (2.5 μg/ml), amikacin (1 μg/ml), and ofloxacin (2 μg/ml), by MGIT 960 system, as per manufacturer's instruction [20,22,23]. H37RV strain was taken as reference for DST.

2.5. Ethical approval

This is retrospective study of the samples collected under national programmatic setting, and patients were not interviewed, thus ethical approval not required.

3. Results

During the three years study period, sputum samples of 35,000 TB suspected patients were examined for mycobacterial investigations. Out of total TB suspected patients 12140 (35%) belonged to ≥60 years (geriatric) age group as shown in Table 1. Among them 13% (1621/12140) were AFB smear-positive and 87% (10519/12140) were smear-negative. The men-to-women ratio among these geriatric TB suspected patients was 10, with 11,041 (91%) men and 1099 (9%) women, and their average age was 71 years. A total of 915 culture results of geriatric TB patients were analyzed conveniently during the study for analyzing drug resistance results, out of which 470 (51%) were positive for *Mtb*, 63 (7%) were contaminated, 36 (4%) were identified as mycobacteria other than tuberculosis (MOTT), and remaining 347 (38%) were culture negative.

A first-line DST results of these 470 *Mtb* culture positive results were reviewed. Of these 470 culture positive geriatric TB patients, 159 were resistant to mono-drug resistant and 210 (45%) strains were identified as MDR-TB, as detailed in Table 2. Among these first-line mono-resistant patterns, maximum number of resistant strains were found to be with isoniazid (134/470, 28%) whereas, rifampicin resistant were observed in least (05/470, 1%). MDR-TB was observed in 30% (23/76) of geriatric TB patients in 2010, 41% (54/130) in 2011, and 50% (133/264) in 2012.

In the present study 240 DST results from geriatric TB patients were reviewed for second (II^{nd}) line anti-TB drugs, i.e., kanamycin, amikacin, capreomycin and ofloxacin. The results revealed that 17 (7%) of these patients had XDR-TB i.e., resistant to at least one of the injectable drugs (kanamycin/ amikacin/ capreomycin) as well as ofloxacin. The XDR-TB was found to be 3% (1/34) in 2010, 4% (2/50) in 2011, 9% (14/156) in 2012. The most common resistant pattern observed was mono-resistant strains, that was with ofloxacin 38/270 (16%) (Table 3).

The age distribution table showed that MDR-TB and XDR-TB strains were more common in age group of 60–65 years, with 157/308 (51%) and 12/157 (8%) respectively. In the age group >75 years, MDR-TB strains were found to be 3/23 (13%), however, no XDR-TB strain was observed in this group. (Table 4).

4. Discussion

Despite the overall decline of TB cases resulting from the implementation of more effective infection control practices, rapid molecular diagnostic tests, directly observed therapy (DOTS), and efforts to control human immunodeficiency virus (HIV) infection, preventive and control approaches among other high-risk groups such as geriatric TB population remain an epidemiological and clinical challenge. As a result, the geriatric TB population has emerged as a potential reservoir of further spread of TB infection [7,24].

Various studies on TB and drug resistance TB have been undertaken

Table 1
Demographic characteristics.

Parameters	Numbers
Total samples (geriatric TB suspects)	12,140
Male	11,041 (91%)
Female	1099 (9%)
Smear positives	1621 (13%)
Culture results among geriatric TB patients	
Total number of cultures reviewed	915
Culture positives	470 (51%)
Contamination	63 (7%)
MOTT	36 (4.0%)

MOTT = Mycobacteria other than tuberculosis, TB = Tuberculosis.

Table 2
Annual distribution of MDR and mono resistant mycobacterial strains in geriatric patients.

Years	No of DST	Mono-resistant Mycobacterial strains				MDR-TB (%)
		S	H	R	E	
2010	76	0	18	0	0	23 (30)
2011	130	3	31	1	2	54 (41)
2012	264	9	85	4	6	133(50)
Total	470	12	134	5	8	210 (45)

DST = Drug susceptibility testing; MDR = Multidrug-resistant; S = Streptomycin; H = Isoniazid; R = Rifampicin; E = Ethambutol. Percent value calculated in round off.

Table 3
Year wise distribution of extensively drug-resistant tuberculosis (XDR-TB) and ofloxacin resistant TB of geriatric TB patients.

Year	Total number of DST	Monoresistant to ofloxacin (%)	XDR-TB (%)
2010	34	6 (18)	1 (3)
2011	50	9 (18)	2 (4)
2012	156	23 (15)	14 (9)
Total	240	38 (16)	17 (7.08)

DST = Drug susceptibility testing, XDR = Extensively drug-resistant, Percent value calculated in round off.

throughout the country, wherein due emphasis has not been given on geriatric TB. No significant microbiological data is available showing the disease burden in geriatric TB patients and status of their drug susceptibility against anti-TB drugs. Morris et al in his study correctly recommended that pulmonary tuberculosis in elderly patients should be considered as a different entity of diseases [25].

To our knowledge this is the first attempt to collect, tabulate and thoroughly analyze the comprehensive data on geriatric tuberculosis. This study highlights the comprehensive data on smear-positive rate, culture positivity and resistance patterns of mycobacterial strains against Ist and IInd line anti-TB treatment (ATT) drugs used for the treatment of geriatric tuberculosis. The present study showed 13 % smear-positives among the total sputum samples screened for TB which is comparable with the institutes' own monthly data result where sputum smear-positives range between 15 and 18% as well as other studies. The frequency of sputum smear-positive was found to be higher (66.8%) in another study [26], because authors reviewed patients who were already registered for TB treatment rather than suspected cases. Our findings are in line with the study conducted by Zhao P et al in terms of detection of MOTT (4% versus 3%), and culture contamination results (7% versus 6%), however, *Mtb* culture positivity was higher in our study (51% versus 43%) [27]. This inconsistency of culture positivity may be due to various regions like selection of patients, inclusion of different age groups etc.

The association between different age groups of geriatrics and occurrence of MDR-TB is not well established and heterogeneity remain very high [28]. Among the geriatric TB patients, we observed MDR-TB and XDR-TB predominantly in the age group of 60–65 years as compared to other higher age group. We found high frequency of mono-resistant with isoniazid as compared to other first line anti-TB drugs, which is consistent with previous study [29]. High frequency MDR and XDR-TB in the present study may be attributed to inclusion of very sick patients from our tertiary care TB hospital which were more likely to be drug resistant. Previous studies described high frequency of fluoroquinolone among MDR-TB/rifampicin-resistant TB (RR-TB) patients [30,31]. The present study observed high frequency of MDR-TB and hence, this may be the reason of high frequency of ofloxacin (a fluoroquinolone) resistance encountered in this study.

The results showed that occurrence of drug resistance in geriatric TB patient is also common finding. Moreover, previous study showed higher frequencies of atypical and radiological presentation, adverse drug reaction and higher TB related death [32]. Therefore, study highlighting the need of special efforts for geriatric TB patients to identify and prompt treatment as they have struggled hard for shaping our future. According to previous retrospective study, most culture positive patients were belong to general community and were living with their family. Whereas, in developed nations the geriatric TB seen in the congregate settings, such as prisons, old age nursing homes, individuals living in home alone and old age patient having chronic lung disease [33,34] and is important concern. Geriatric tuberculosis also constitutes a significant number which may be a potential source of infection in community and need special attention in order to give a boost to success of NTEP. The study has some limitations; it did not fully cover the review of culture and DST results of all 12,140 geriatric TB suspected patients. Culture and DST results reviewed according to convenient and therefore, number of these results is not uniform among all three years. Detailed demographic information were also not analyzed.

5. Conclusion

The study clearly shows the high number of MDR/XDR among geriatric TB patients at tertiary care TB hospital. A separate line of early identification, diagnosis and treatment of geriatrics be evolved without further loss of time. Suitable action should be taken at the programmatic level to protect our geriatric patients from the tuberculosis. However, further study with large sample size is needed to confirm the findings.

Authors contributions

Conception and design of the study: AKV, RKD, RNY.
Acquisition analysis and interpretation of data: AKV, GK, RNY.
Drafting the manuscript: AKV, GK.
Revising the manuscript critically for important intellectual content: RNY, AKV.
Final approval of the version to be submitted: RKD, AKV, GK, RNY.

Table 4
MDR and XDR mycobacterial strains in different age group of geriatric TB patients.

Age group	1st Line DST (n = 470)						2nd Line DST (n = 240)		
	No of DST	Mono S (%)	Mono H (%)	Mono R (%)	Mono E (%)	MDR-TB (%)	No of DST	Mono Ofloxacin (%)	XDR-TB (%)
60–65	308	7 (2)	111 (36)	4 (1)	5 (2)	157 (51)	142	26 (18)	12 (8)
66–70	98	3 (3)	12 (12)	1(1)	2(2.04)	36 (37)	67	6 (9)	4 (6)
71–75	41	2 (5)	7(17)	0 (0)	1 (2)	14 (34)	24	5 (21)	1(4)
>75	23	0 (0)	4 (17)	0 (0)	0 (0)	3 (13)	7	1 (14)	0 (0)
Total	470	12 (3)	134 (28)	5 (1)	8 (2)	210 (45)	240	38 (16)	17 (7)

MDR = Multidrug-resistant tuberculosis, XDR = Extensively drug-resistant. DST; Drug Susceptibility Testing. Age 60 years or above considered as geriatric. Percentage value calculated horizontally.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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