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Original Research Article

A Cross Sectional Study of Risk Factors and Prevalence of Drug Resistance in Tuberculosis Cases from Tertiary Care Hospital, Bengaluru Rural

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Abstract:

Introduction: Tuberculosis affects people all around the world especially Indian population as pulmonary and extrapulmonary tuberculosis. It's caused by acid fast bacilli called Mycobacterium tuberculosis and the emerging drug resistance has made the scenario more cumbersome. We have a National Tuberculosis Elimination Program (NTEP) for controlling tuberculosis and with introduction of Cartridge Based Nucleic Acid Amplification testing (CBNAAT) to the district centre as a part of Universal Drug Susceptibility testing (UDST) under NTEP regular check on the tuberculosis cases and drug resistance is becoming a reality.

Aim: To estimate the prevalence of tuberculosis and its drug resistance in the rural population, under our DMC.

Material and Method: All the details of the patients including the address, phone number, Aadhar card details, the HIV status and random blood sugar results were documented. Each patient was registered in NIKSHAY portal and NIKSHAY number was generated. The samples were collected in duplicate in Falcon tubes and processed in our Designated Microscopy Centre (DMC) by Ziehl Neelsen staining and sent to district center for CBNAAT. Further testing was done in Intermediate TB reference laboratory/National Tuberculosis Institute Bangalore depending on the CBNAAT results.

Results: A total of 799 patients' samples were received from Jan 2018 to December 2022 -a period of 5years and 8 cases were diagnosed based on radiodiagnosis with positivity rate of 19.3%. Pulmonary tuberculosis accounted for 82.05% and remaining were extra pulmonary tuberculosis cases 17.96%. Tubercular lymphadenitis in female staff nurses in the age group of 20-30years with history of contact with TB positive patients who were under their care for few days was a significant finding. Prevalence of drug resistance was very low in our study accounting to just 2.09%. Out of the 156 positive tuberculosis cases 3 had HIV co - infection and 28 had diabetes mellitus. Males (72.43%) were more compared to females, with age group of 35-54yrs having the maximum positive cases accounting to 34.61%.

Conclusion: In our study we estimated the prevalence of tuberculosis and its drug resistance, which was the first of its kind from our area. The importance of CBNAAT was evident as many cases missed by microscopy were picked up CBNAAT and the early detection of drug resistances aided the change in regimen which is very important to control the spread of multi- drug resistance tuberculosis. Our sample size was small because of the lockdown period and due to the social stigma of tuberculosis which exists especially in rural areas. The overall results and significant findings such as tubercular lymphadenitis in our nursing staff will aid the policy makers of the NTEP to enhance active case findings, prophylaxis in tuberculosis and other changes as suggested in the limitation section of our study.

Keywords: Tuberculosis, Mycobacterium tuberculosis, CBNAAT, Extrapulmonary Tuberculosis.

Introduction

Tuberculosis (TB) is caused by Mycobacterium tuberculosis complex (MTB) which is a major cause of morbidity and mortality affecting millions of people from time immemorial. [1] India accounts for 27% of total estimated TB cases worldwide.[2] It affects the lung primarily as pulmonary tuberculosis accounting for 60-90% and other organs as extrapulmonary tuberculosis constituting 10-40% of all TB cases. The percentage of extrapulmonary cases is higher up to two thirds in Human immunodeficiency virus (HIV) patients. Tubercular lymphadenitis (35%) is the most common form of extrapulmonary tuberculosis. The sites commonly affected are posterior cervical and supraclavicular.[1] An increase in multi-drug resistance (MDR) in tuberculosis has made the situation more worrisome. India accounts for about one fourth of

the total MDR TB cases worldwide. [3] The prevalence of tuberculosis and its drug resistance from various parts of India is essential for the success of National TB program. Our institute was made a Designated Microscopy Centre (DMC) in January 2018 under Revised National Tuberculosis Control Program (RNTCP) which was renamed to National Tuberculosis Elimination Program (NTEP). This study was conducted with the primary objective of estimating the prevalence of tuberculosis and its drug resistance in the rural population, under our DMC.

Material and Methods:

This was a cross sectional study carried out in the Department of Microbiology, Akash Institute of Medical Sciences and Research Centre, Bengaluru rural in liaison with district tuberculosis Centre, Intermediate TB reference laboratory and National Tuberculosis Institute, Bangalore from January 2018 to December 2022 ,a period of 5years. Ethical clearance for the study was obtained from the Institutional Ethics Committee with reference no IEC NO: AIMSRC/IEC/03/2023-24.

The samples in duplicate were collected in Falcon tubes (2 samples from each patient) for TB testing. For sputum sample, spot-early morning or two supervised spot specimens at least one hour apart were collected. Sputum sample with salivary contamination, inadequate samples (less than 3ml), tissue sample in formalin were rejected and a repeat sample was requested wherever possible. Ziehl Neelsen (ZN) staining was done from each sample. All samples were transported in triple layered package in cool chain temperature maintained at 8˚C to 20˚C for Cartridge Based Nucleic Acid Amplification testing (CBNAAT) to the district centre as a part of Universal Drug Susceptibility testing (UDST) under NTEP. The UDST was introduced in 2017 and implemented officially in Karnataka from April 2018. If CBNAAT result is MTB detected, the second sample is sent to Intermediate TB reference laboratory/National Tuberculosis Institute Bangalore for further testing.

The further testing depends on the CBNAAT result. If CBNAAT results rifampicin as sensitive, second sample is sent for first line Line Probe Assay (LPA) to look for isoniazid resistance. If isoniazid is sensitive, then drug sensitive TB drug regimen was continued (other first-line anti-TB drugs susceptibility is not known) and if isoniazid resistance is detected then it was subjected to second line LPA. If rifampicin is resistant, then the sample was subjected to first- and second-line LPA. If resistance is detected in second -line LPA further testing was done using liquid culture and drug susceptibility testing (CDST) to test for resistance to individual or additional drugs (moxifloxacin, kanamycin, capreomycin and linezolid). At each step the drug regimen was modified according to the drug susceptibility results which were followed up by our Tuberculosis Health Visitor (TBHV). If LPA is not able to provide a valid result or in case of smear-negative samples, the samples were cultured, and LPA is run on the culture isolates. The laboratory turnaround time for CBNAAT is 2 hours, for both the LPAs is 72 hours and for liquid CDST is 42 days. [4,5] The previously treated TB cases samples were upfront tested for rifampicin and isoniazid susceptibility.

Extrapulmonary samples and some pulmonary samples were subjected to other tests like bacterial culture and sensitivity, histopathology, adenosine deaminase testing, cell count and cell type as per the sample type and clinician's request. The details of the patients including the address, phone number, Aadhar card details, the HIV status and random blood sugar results etc were documented. Each patient was registered in NIKSHAY portal and NIKSHAY number was generated. Statistical analysis: The data obtained was entered and analysed using Microsoft Excel

Result

A total of 799 patients' samples (2 samples from each patient) were received from Jan 2018 to December 2022(5 years).

Out of the 799 samples,708 were pulmonary samples and 91 were extrapulmonary: 9 pus, 29 pleural fluid, 15 CSF, 12 peritoneal fluid ,19 lymph node tissue (FNAC sample),3 gastric lavage, 2 urine, 1synovial fluid, 1 Abdominal drain. Nine out of 799 samples were from previously treated cases of which only 4 were positive. One hundred and forty-three (143) patients were diagnosed and confirmed by lab investigations. Five cases (5) were diagnosed clinically with no laboratory confirmation. The clinically diagnosed cases were 1 pulmonary tuberculosis, 3 pleural effusion, 1 cervical lymphadenopathy. Eight cases (8) were diagnosed by radiodiagnosis which includes 1 miliary tuberculosis, 3 abdominal tuberculosis case, 4 vertebral tuberculosis case. A total of 156 cases were considered positive and given anti-tubercular treatment. The positivity rate of tuberculosis in patients visiting our DMC was calculated as 19.3 % (156/807[799+8] x100) which includes both pulmonary (128cases/ 82.05%) and extra pulmonary tuberculosis (28 cases /17.96%). The age and gender distribution of the cases are illustrated in Table 1 and Table 2respectively.

Table 1: Age distribution of TB cases (total 156cases)

Age group	Percentage
<15yrs	3.20%
15-34rs	30.76%
35-54yrs	34.61%
>55yrs	31.41%

Table 2: Gender distribution of TB cases (total 156cases)

Gender	Percentage
Male	72.43%
Female	27.56%

Table 3: The investigations which were positive for confirmation of tuberculosis including radiodiagnosis [total of 151 cases (143+8)]

Investigation	Micros-copy only	CBNAAT only	Histopatholo-gy only	Radiodiag-nosis only	Microsco-py and CBNAAT	CBNAAT And Histopathol-ogy
Positive cases	2	30	4	8	101	6

Among the 11 extrapulmonary samples from lymph node ---6 were CBNAAT and histopathological positive and 4 were only positive on histopathology and 1 was clinically diagnosed. Four cases of Tubercular lymphadenitis were of female staff nurses (freshers) in the age group of 20-30years with history of contact with TB positive patients who were under their care for few days. Among the 4 staff nurses one was positive on histopathology but CBNAAT negative. The remaining 3 were CBNAAT positive as well was positive on histopathology. All the cases were given anti-tubercular treatment and showed clinical improvement.

The drug resistance was detected in only 3 patients (2.09%), isoniazid resistance (1.39%) in 2 patients 1 previously treated and 1 new case of TB and 1 Rifampicin resistance 0.69% in previously treated patients. Both the cases which were previously treated were documented as lost to follow up as per their earlier records. Out of the 156 positive tuberculosis cases 3 had HIV co- infection and 28 had diabetes mellitus.

Discussion

The RNTCP started in 1997 with the incorporation of Directly Observed Treatment Supervised (DOTS) as a main pillar in TB treatment. Studies covering the rural areas of south India reported a decrease in the first few years of implementation of DOTS. [6,7] A subsequent rise thereafter could be because of increase in case finding or increase in the risk factors like low socio -economic condition, alcohol and smoking consumption, diabetes and HIV, but evidence was not established.[6]

The recent survey conducted nationwide in India for estimating the burden of TB cases from 2019 to 2021 reported the crude prevalence infection as 31.3% among cases aged 15 years and more. The microbiologically confirmed pulmonary cases ≥15years of age was 316 per lakh population. The prevalence of all forms of TB was estimated to be 312 per lakh [8] The prevalence rate in our study in our population was also 312 per lakh population as per the data collected which was for 50,000 population which includes lab confirmed cases (microbiological, histopathological, and radiodiagnosis) as well as clinically diagnosed cases. The meta- analysis study of various Indian publications on prevalence of pulmonary tuberculosis from period of 1997 to 2018[2] and national survey 2019-2022 [8] showed an increase in cases of TB in males which was like our study. The positive cases in our study were maximum in the age group of 35-54years which was different from other study [6] in which the maximum tuberculosis cases were above 55years of age and 25-34 age group in the national survey [8]. There was only a slight increase in this age group of 35-45 years and the other age group categories that is 15-34 years and >55 years had equal distribution of positive tuberculosis case as shown in Table 1.

There were 3 TB cases which showed drug resistance and 2 out of 3 had history of prior TB treatment which was same as other studies which established prior treatment as main risk factor. [3,8,9,10,11] The national survey of year 2022 reported MTB detection in 22% cases in which CBNAAT was done and among which 8% was Rifampicin resistant. The introduction of UDST under the NTEP program and its implementation in Karnataka is very essential to meet the goal of End TB by 2025 set by Ministry of Health and Family Welfare. To curb the emerging drug resistance not only the testing but follow up and revision of regimen as per the susceptibility report is very important which can only be done by a dedicated and accountable personnel like the TB Health Visitor (TBHV) appointed for each DMC.

Tuberculosis patient with diabetes in our study was 17.94% (28 positive cases) compared to National survey of year 2022 which was 14.1% in Karnataka and 7.8% overall in India. Tuberculosis and HIV co infection were present in 3 patients. The association of diabetes and tuberculosis is bidirectional that is, TB results in impaired glucose tolerance resulting in diabetes and diabetic patients impaired immune system make them more prone for tuberculosis reactivation. [12,13,14] The other major risk factor for tuberculosis is HIV, which leads to immune suppression resulting in reactivation of latent TB and rapid progression of active TB.[12] Tuberculosis co-infection is the commonest and main cause of mortality in HIV patients. [15] The drug resistance especially Rifampicin is due to malabsorption of the drug and increase adverse effects in HIV patients resulting in non-adherence to treatment and therefore drug resistance. [16,17]

Tubercular lymphadenitis is most common form of extrapulmonary tuberculosis showing a female preponderance and in the age group of 20-40years as established by various studies which was in concordance to our study. [18,19] There was no history of previous history of tuberculosis in our 4 tubercular cervical lymphadenitis cases who were staff nurses who were relatively healthy individuals. All of them had a history of contact with TB patients who were under their care for a period of 2 to 7 days. The main presentation was single painless, lymph node enlargement with associated fever, which occurred in the span of 2 months (year 2018). They were given 6 months drug sensitive tuberculosis regimen. No other occurrence of such an outbreak was reported in the future course of this study.

There is an increased risk of tuberculosis in health care staff compared to community due to the constant exposure to TB cases in a hospital set up. The explanation on why tubercular lymphadenitis occurred in these 4 individuals and during that period is beyond the scope of this study. This outbreak emphasised the importance of effective airborne precautions like using N 95 masks as well as implementation of other managerial, administrative and engineering controls while harboring TB cases in hospitals (TB wards) to prevent further transmission. [20,21]

Limitation

Our sample size was small probably because there is still a social stigma of tuberculosis which exists especially in rural area and an active case finding as a part of NTEP and educating people regarding the early diagnosis and treatment of tuberculosis on a regular interval is very much required. Secondly during the lockdown period, the patient coming to the hospital as well as community activities were reduced markedly. The TBHV is important personnel for the NTEP program success. By the end of year 2020 we had no TBHV so it became very difficult to follow up the patients. A new TBHV was appointed only by March 2024. Lastly though the CBNAAT and LPA have turnaround time of 2 hrs and 3 days respectively, due to the time taken for transport for CBNAAT and LPA the turn-around time gets extended up to 5days which can be overcome by providing CBNAAT/Trunaat to more centres under NTEP. Another suggestion would be to make it mandatory as per National Medical Commission for all medical colleges to buy the CBNAAT/ Trunaat machines at a subsidised price.

Conclusion

In our study we estimated the prevalence of tuberculosis and its drug resistance, which was first of its kind from our area. Our study coincided with the introduction of UDST in Karnataka and therefore the effectiveness of the same was evident from our study as early capture of resistant cases was made possible. The tubercular lymphadenitis in healthy staff nurses who were in contact with TB patients during our study needs to be further analysed and hopefully will aid policy makers to initiate new protocols for prophylaxis in tuberculosis.

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