INDIAN JOURNAL OF TUBERCULOSIS

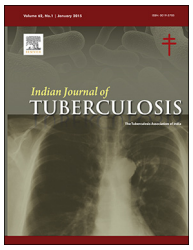
EDITORIAL BOARD

INDIAN JOURNAL OF TUBERCULOSIS 63 (2016) 67–68

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Editorial

Challenges in the diagnosis of extrapulmonary tuberculosis

It is not unusual to find it stated that the scarcity of good diagnostic tools is at the root of the problem that extrapulmonary tuberculosis is likely under-diagnosed in many settings. We submit that the perhaps even more important cause for under-diagnosis of extrapulmonary tuberculosis is the failure of busy clinicians to think of it, most notably if it takes one of the protean yet rare manifestations of tuberculosis. Numerous case reports over the years in the *Journal* have testified to that.

A comprehensive assessment of the secular trends in diagnosis and notification of extrapulmonary tuberculosis under the RNTCP has been published from Delhi a few years ago.[1] It showed that on average about 20% of the cases diagnosed from 1997 through 2002 had tuberculosis at an extrapulmonary site and that the relative contribution to all incident cases increased almost regularly over the period of observation. Half of these cases were peripheral lymphatic and another 30% were pleural. All other sites contributed each fewer than 10% of the total. Thus, 80% of all identified cases of extrapulmonary tuberculosis comprised of what diagnostically might be called either a very easy diagnosis (peripheral lymphatic) or a very difficult diagnosis (pleural effusion).

Any skilled clinician who has seen a dozen or so cases of peripheral lymphatic tuberculosis will have both high sensitivity and high specificity in diagnosing the condition clinically: both the history and the clinical presentation are quite characteristic, notably so if there is a delay in presentation.

Conversely, the etiology of a pleural effusion is clinically difficult to determine and laboratory support is of equivocal assistance in many cases. Barring pleural biopsy,[2] most other diagnostic traditional laboratory approaches often prove futile.

The ease of use and the promising results of the Xpert MTB/RIF® assay have of course also led to the evaluation of the assay for the diagnosis of pleural effusion,[3–5] but not unexpected, the results are generally dismally poor.

It is perhaps a bit over-simplifying, but it appears that for the most common extrapulmonary manifestation in India (and other countries), peripheral lymphatic tuberculosis, experienced clinicians rarely need additional laboratory support if they think of tuberculosis in the first place; for the second most common manifestation, pleural effusion, both classical approaches (culture techniques) and modern nucleic acid amplification techniques (e.g. Xpert MTB/RIF®) perform so poorly that their use is quite possibly not even worth the cost. Unfortunately, the diagnosis will have to rely on the use of chemical and cell analysis of the fluid, combined with clinical judgment and empirical treatment. Where available, the most promising approach to a sensitive diagnosis has been[6] and remains histologic examination of a pleural biopsy specimen.[7] Where tuberculosis is a prevalent cause of pleural effusion, a characteristic histology is also reasonably specific.

Rarer forms of extrapulmonary tuberculosis include the highly fatal central nervous system manifestations, notably meningeal tuberculosis. The World Health Organization recommends the use of the Xpert MTB/RIF® assay for the diagnosis of tuberculous meningitis.[8] Some experts caution against relying too much on it,[9] arguing that the negative predictive value has to be set very high for such a lethal condition, much higher than what this test can offer. In consequence, then, common sense will prevail when clinicians – as with other bacteriological examinations such as microscopy and culture – remain wary of potentially false-negative results and will not shy away from initiating anti-tuberculosis treatment when in doubt.

The immunosuppression caused by HIV infection leads to an excessively high frequency of disseminated tuberculosis which is highly fatal if undiagnosed and thus left untreated.[10] Blood cultures for *Mycobacterium tuberculosis* have poor sensitivity and the diagnostic delay is unacceptably long for a condition that is so rapidly fatal.[11] The experience with the Xpert MTB/RIF assay from blood samples is limited, but the little that is known suggests that it has also very poor sensitivity[12] and is thus of little usefulness for all practical purposes. The most efficient approach remains early diagnosis of HIV infection, followed by prompt anti-retroviral treatment to prevent progression to disseminated tuberculosis that is barely amenable to timely and accurate diagnosis.

In summary then, fortunately the most common extrapulmonary manifestation of tuberculosis, peripheral lymphatic tuberculosis, allows an accurate clinical diagnosis if the clinician has experience and retains a high index of suspicion. The diagnosis of tuberculous pleural effusion remains as difficult as it has always been and molecular laboratory techniques have not changed that at all. Unfortunately, the same goes for the most lethal forms of extrapulmonary tuberculosis, meningeal, and disseminated: the clinician remains pretty much left to his or her own devices of making a clinical diagnosis on not much more than clinical presentation and careful history taking. Laboratory tests that provide sensitive and specific diagnosis for these latter conditions remain at present still out of reach.

Conflicts of interest

The author has none to declare.

REFERENCES

1. Arora VK, Gupta R. Trends of extra-pulmonary tuberculosis under Revised National Tuberculosis Programme: a study from south Delhi. *Indian J Tuberc.* 2006;53:77–83.
2. James P, Gupta R, Christopher DJ, Balamugesh T. Evaluation of the diagnostic yield and safety of closed pleural biopsy in the diagnosis of pleural effusion. *Indian J Tuberc.* 2010;57:19–24.
3. Porcel JM, Palma R, Valdés L, Bielsa S, San-José E, Esquerda A. Xpert® MTB/RIF in pleural fluid for the diagnosis of tuberculosis. *Int J Tuberc Lung Dis.* 2013;17:1217–1219.
4. Meldau R, Peter J, Theron G, et al. Comparison of same day diagnostic tools including gene Xpert and unstimulated IFN-g for the evaluation of pleural tuberculosis: a prospective cohort study. *BMC Pulm Med.* 2014. http://dx.doi.org/10.1186/1471-2466-14-58.
5. Rufai SB, Singh A, Kumar P, Singh J, Singh S. Performance of Xpert MTB/RIF assay in diagnosis of pleural tuberculosis by use of pleural fluid samples. *J Clin Microbiol.* 2015;53:3636–3638.
6. Deshmukh MD, Virdi SS. Pleural punch biopsy in tubercular pleural effusions – to find out comparative value of single and multiple specimens. *Indian J Tuberc.* 1972;19:95–100.
7. Light RW. Update on tuberculous pleural effusion. *Respirology.* 2010;15:451–458.
8. World Health Organization. *Automated Real-Time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF Assay for the Diagnosis of Pulmonary and Extrapulmonary TB in Adults and Children. Policy Update. World Health Organization Document WHO/HTM/TB/2013.16.* 2013;1–79.
9. Boyles TH, Thwaites GE. Appropriate use of the Xpert® MTB/RIF assay in suspected tuberculous meningitis. *Int J Tuberc Lung Dis.* 2015;19:276–277.
10. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS.* 2015;29:1987–2002.
11. Archibald LK, den Dulk MO, Pallangyo KJ, Reller LB. Fatal *Mycobacterium tuberculosis* bloodstream infections in febrile hospitalized adults in Dar es Salaam, Tanzania. *Clin Infect Dis.* 1998;26:290–296.
12. Feasey NA, Banada PP, Howson W, et al. Evaluation of Xpert MTB/RIF for detection of tuberculosis from blood samples of HIV-infected adults confirms *Mycobacterium tuberculosis* bacteremia as an indicator of poor prognosis. *J Clin Microbiol.* 2013;51:2311–2316.

Hans L. Rieder MD, MPH[a,b,*]
[a]*Tuberculosis Consultant Services, Kirchlindach, Switzerland*
[b]*Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland*

[*]*Correspondence to*: Tuberculosis Consultant Services, Kirchlindach, Switzerland

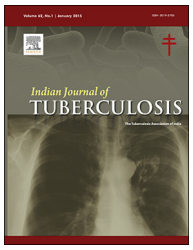
Available online 16 June 2016

http://dx.doi.org/10.1016/j.ijtb.2016.05.013
0019-5707/

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Viewpoint

Based on speech delivered during 3rd Conference of South East Asia Region of The Union 26th and 27th May, 2016 Kathmandu (Nepal)

His Excellency Nanda Bahadur Pun ''Pasang'' (Vice President)

TB and lung disease has not decreased as expected. Not only in Nepal, but worldwide especially in the least developed countries of the Third World, it has been a massive health issue. Many efforts have been made to control tuberculosis. A contingent of health workers from ASEAN countries have been battling against TB day and night. I praise this good deed of you all in open voice. I thank you all associations and health workers committed with the ASEAN countries.

Nepal has been taken so many steps to abolish tuberculosis from the nation. For this not only from government sector but also from public level efforts have been made. Since Bikram Sambat 2010 Nepal Tuberculosis Abolishment Organization became active in abolishing TB and it started international relation and has extended hands with government in the field. I openly admire the efforts made by this organization.

Consumption of tobacco has been the main cause of TB. Tuberculosis which can be transmitted through respiration has been main public problem. This disease has claimed thousands of lives annually worldwide. In a country like Nepal it has been revealed fact that thousands of people are affected by such disease. Many healthy people are infected by this disease. Every year around 5000 Nepalese people lose their lives by this disease. This is a great challenge.

Due to the increase in public awareness and scientific development in one hand such diseases are remarkably controlled. This is good news for the human race. But on the other hand, the emergence of ''multi drug resistance tuberculosis'' has been a challenge for the scientists, doctors and social workers involved in this field. I hope this conference will find a way to face this defiance. The world has been globalized. Along with this efforts has been made to solve common problems which is very necessary and praise worthy deed to face present challenges ''Joint efforts for Common problems'' is only remedy. Contagious disease cannot be stopped by any country's boundary.

There can be no second thought that diseases transferred by respiration is the common problem of the world. I hope that this third conference of The Union of ASEAN against Tuberculosis will find a way to solve the problems caused in the lives of ASEAN people and will further promote public awareness and treatment in more effective and public oriented ways and it will be a milestone in this work.

Prevention is better than cure. I have already mentioned, the cause of TB and its incurability is consumption of Tobacco related goods. Nepal has promulgated and implemented mentionable policies to control the consumption of tobacco related goods which is admired by world community. ''Ninety percent pictorial health warning'' strategy adopted by Nepal is an example for the world. Besides this the government has forbidden to smoke in public places. Ultimately it is an effort to control tuberculosis. Implementing this strategy successfully and following the ''plain packaging'' strategy forwarded by the WHO we need to over tax and price on tobacco related goods to stop the youth and children from its consumption is the urgent and effective way. I believe, this will inspire other countries fighting against TB.

The new constitution of Nepal has assured every citizen the right to get free health service emphasizing on research to make health service everywhere available and qualitative, the state has adopted the policy of increasing health organizations and health workers.

Conflicts of interest

The author has none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.008

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

A cross sectional study in patients with confirmed spinal tuberculosis in central Taiwan: Analysis of preliminary clinical presentation and neuroradiological findings

Chang-Hua Chen [a,*], *Chih-Wei Lee* [b], *Jui-Kuo Hung* [c], *Yu-Jun Chang* [d], *Chun-Yuan Cheng* [e], *Yu-Min Chen* [f]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*
[b] *Department of Medical Imaging, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*
[c] *Department of Orthopedic Surgery, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*
[d] *Epidemiology and Biostatics Center, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*
[e] *Division of Neurosurgery, Department of Surgery, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*
[f] *Department of Pharmacy, Changhua Christian Hospital, Changhua, 135 Nanhsiau Street, Changhua, Taiwan, ROC*

ARTICLE INFO

Article history:
Received 19 March 2015
Accepted 13 May 2016
Available online 14 July 2016

Keywords:
Spine
Tuberculosis
Preliminary clinical presentation
Preliminary neuroradiological findings

ABSTRACT

Spinal tuberculosis (STB) can cause significant functional impairment. The purpose of the present study was to analyze the factors at preliminary presentation and the neuroradiological findings in STB patients. We performed a retrospective cross-sectional analysis of cases with a definitive diagnosis of STB. Four patients with confirmed mycobacterial infection and histopathological findings confirming TB were identified. We noted two key clinical indicators. We also identified seven key neuroradiological findings associated with STB lesions. A high degree of clinical suspicion along with nine neuroradiological findings described in this study are important for STB diagnosis and for starting treatment with antituberculosis agents.

1. Background

Tuberculosis (TB) is an ancient disease, but is still a major public health problem globally.[1] The incidence of TB appears to be increasing throughout the world.[2] Although pulmonary tuberculosis (PTB) is the most common form, extrapulmonary tuberculosis (ETB) also causes significant morbidity and mortality. In Taiwan, the estimated TB burden was 44/million/year in 2009.[3] Spinal tuberculosis (STB) comprises

* *Corresponding author*. Tel.: +886 47238595.
E-mail address: chenchanghuachad@gmail.com (C.-H. Chen).

Abbreviations: AFS, acid fast stain; ATA, antituberculosis agents; CCH, Changhua Christian Hospital; CCHS, Changhua Christian Hospital System; CT, computed tomography; ETB, extrapulmonary tuberculosis; FNAC, fine needle aspiration cytology; HERZ, isoniazid, ethambutol, rifampin, and pyrazinamide; MRI, magnetic resonance imaging; PTB, pulmonary tuberculosis; STB, spinal tuberculosis; TB, tuberculosis.

http://dx.doi.org/10.1016/j.ijtb.2016.05.014

1–4.3% of all TB cases and 10–15% of all ETB cases.[4] Because STB has been suggested as an important cause of vertebral osteomyelitis and it is a common site of ETB, we conducted a literature review on STB (summarized in Additional File). However, physicians are not only familiar with the common clinical features of STB, but have an in-depth understanding of the disease; an early diagnosis and effective treatment can minimize the occurrence of sequelae and improve clinical outcomes. Since the clinical symptom of STB is variable, and some of fragile patients developed handicapped, such as spinal cord compression, to study the accurate and effective diagnosis and treatment of STB are very necessary. Literature is sparse concerning the early preliminary clinical presentation and neuroradiological findings of STB; therefore, the purpose of the present study was to analyze these factors.

2. Materials and methods

2.1. Hospital setting and data collection

The population of rural area of central Taiwan is mostly served by the Changhua Christian Hospital System (CCHS), which totally has 4000-bed to serve patients. Changhua Christian Hospital (CCH) is one of nine branch hospitals among the CCHS, and it is an 1800-bed tertiary referral medical center situated in central Taiwan. This study was carried out at CCHS and was approved by the institutional review board of CCH. From January 2010 to December 2013, hospitalized patients over 18 years of age who were diagnosed with STB were included in this study. The study design was retrospective in

Table 1 – Preliminary clinical presentation and preliminary neuroradiological findings.

Patient	1	2	3	4
Age (year)/sex	78/F	66/M	82/F	57/M
Previous exposure to TB	NEG/NEG	NEG/NEG	NEG/NEG	POS/NR
Hypertension/diabetes mellitus/acupuncture	POS/NEG/NEG	POS/NEG/NEG	NEG/NEG/NEG	NEG/NEG/NEG
Previous spinal disorders	ST, L4/L5; CF, L5	ST, s/p TSF	CF L2/3, s/p VTB	NEG
Previous prednisolone usage	NEG	NEG	NEG	POS
Patient delay (days)/doctor delay of ATA (days)/total delay (days)	60/5/65	30/5/35	32/5/37	60/3/63
Local painful sensation on admission	2 Mo	1 Mo	NEG	2 Mo
Fever on admission	NEG	NEG	NEG	4 days
Wound discharge on admission	NEG	POS	NR	NR
Neurological deficits on admission	NEG	NEG	right lower LW	right FP
American Spinal Injury Association impairment score on admission	A	B	B	A
Evidence of pulmonary TB on chest plain film radiography on admission	NEG	NEG	NEG	NEG
White cell count (cell/mm^3) on admission	4800	6200	5800	6800
ESR (mm/h) on admission	NR	45	NR	68
GOT/GPT (U/L) on admission	40/35	41/44	35/25	36/46
Ccr (mL/min) on admission	50	60	50	65
Uric acid (mg/dL) on admission	5.5	5.6	6	5.6
CRP (mg/dL) on admission	24.9	NR	NR	5.5
TB smear of sputum	NEG	NEG	NEG	NEG
TB smear of tissue/MtbcDT of tissue/TB culture of tissue	POS/POS/MTBC	POS/POS/MTBC	POS/POS/MTBC	POS/POS/MTBC
Interferon	NR	NR	NR	POS
Histopathological results	GI	GI, CN	GI, CN	GI, CN
Preliminary neuroradiological findings				
Originate from vertebral endplate	OBS	OBS	OBS	OBS
Involves the anterior vertebral body corner	OBS	OBS	OBS	OBS
Subligamentous spread	OBS	OBS	OBS	OBS
Multiple vertebral bodies involved and preserved disk	OBS	OBS	OBS	OBS
Extensive paraspinal abscess formation	OBS	OBS	OBS	OBS
Calcification of abscess		OBS		
Vertebral destruction, vertebral body collapse (Gibbus deformity)	OBS	OBS	OBS	OBS
Chest plain film radiography findings	Non-specific	Non-specific	Non-specific	*1

Abbreviations: ATA: anti-tuberculosis agent; Ccr: creatinine clearance rate; CF: compression fracture; CN: caseous necrosis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; F: female; FP: flank pain; GI: granulation inflammation; GOT: glutamate oxaloacetate transaminase; GPT: glutamate pyruvate transaminase; M: male; Mo: month; MTBC: *M. tuberculosis* complex direct test; MtbcDT: *M. tuberculosis* complex direct test; NEG: negative; NR: not recorded; OBS: the finding was observed; POS: positive; s/p: status of post; ST: spinal stenosis; TB: tuberculosis; TSF: transpedicular screws fixation; VTB: vertebroplasty.
Notes: *1 linear fibrosis with a dense nodule in the right upper lobe due to previous pulmonary tuberculosis.

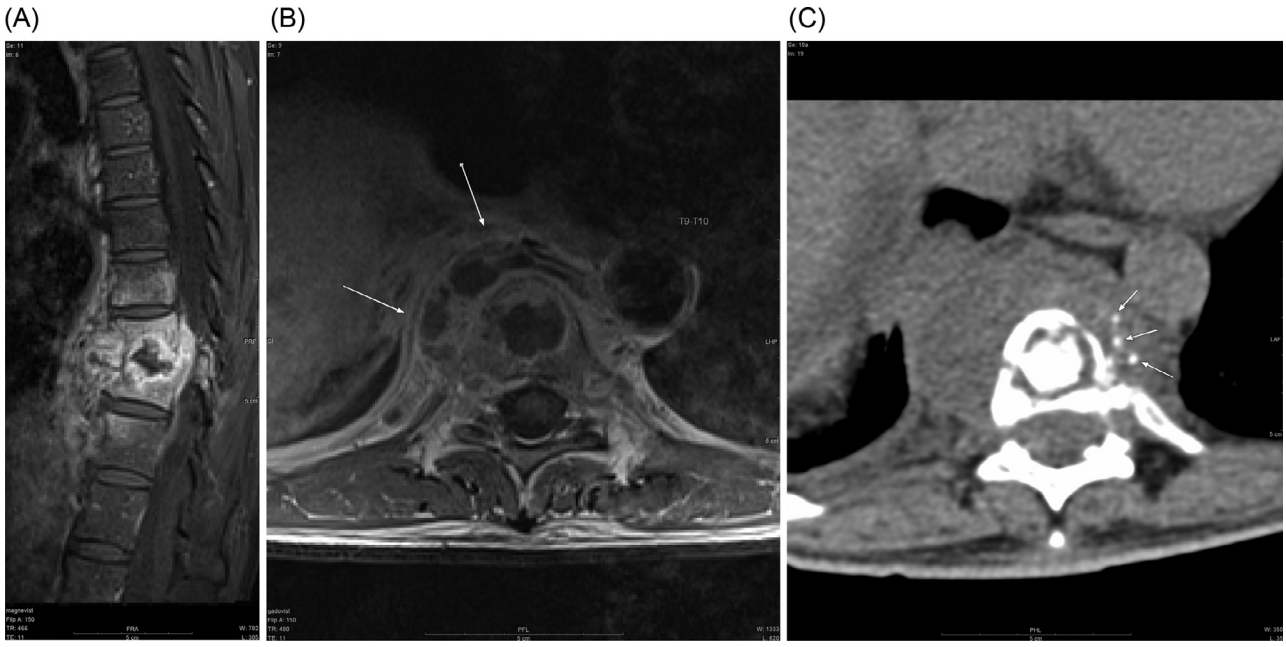


Fig. 1 – The neuroradiological findings of a patient with spinal tuberculosis. (A) Post-gadolinium T1-weighted MR imaging with fat saturation, sagittal view, showed enhancement of the T9 and T10 vertebrae with apposing endplates erosion, and enhancing soft tissue spreading along the anterior subligamentous space, from T7 to T12 level. Mild enhancement of the T8 inferior and T11 superior vertebral bodies are also noted, but the T8/9 and T10/11 discs are preserved. (B) Post-gadolinium T1-weighted MR imaging with fat saturation, axial (at T9–10 level) view, showed extensive paraspinal abscess (arrow). (C) CT scan of the thoracic spine axial view showed calcification of the paraspinal abscess (arrow).

nature and the data were collected throughout the 4-year study period. All adult patients (>18 years) diagnosed with STB by ALL of the following methods were included: positive vertebral osseous acid fast stain (AFS), positive TB culture from fine needle aspiration cytology specimens, and characteristic pathologic findings. All patients with an STB diagnosis received standard anti-tuberculosis agents (ATA), according to the Taiwanese guidelines for TB diagnosis and treatment.[5] We used descriptive statistical method to analyze the dataset.

3. Results

Five cases were diagnosed as spinal mycobacterial infection during the study period. Four cases with confirmed mycobacterial infection and histopathological findings confirming TB were identified, and another one case is non-tuberculosis mycobacterial infection. Only four patients with confirming STB were enrolled in this study. The preliminary clinical presentations and initial neuroradiological findings of patients with a definitive diagnosis of STB are listed in Table 1. Two patients were men and 2 were women, with ages ranging 57–82 years. One patient had a prior history of TB, and another patient had PTB as a comorbidity. Three patients had previous spinal disorders before STB. The total delay time ranged 25–65 days. Two patients had neurological deficits initially, which were reversed by the end of the study period. One patient presented with a fever and 2 presented with back pain. The initial laboratory data showed no significant abnormalities except for elevated levels of serum C-reactive protein. The neuroradiological findings of a patient with STB are shown in Fig. 1. All patients received standard ATA, and they all survived.

4. Discussion

To our knowledge, this is the first study to analyze the initial clinical presentation and neuroradiological findings of STB patients in central Taiwan. We observed that the elderly are particularly susceptible to STB, as the average age of the patients in this study was 70.8 years. Similarly, Weng et al. reported that 55% of the STB patients in their study were older than 70 years.[6] In our study, an equal sex distribution was observed, which is similar to that in previous literature (men = 53% in Additional File).

STB has a wide variety of manifestations. However, we disclose 2 key signs of STB (Table 1), which was consistent with observations in previous reports.[6] In a previous study by Jutte et al., in the Netherlands, there was a mean delay in the diagnosis of nonspinal bone and joint TB of 35 weeks.[4] In this study, the duration of total delay ranged 25–65 days. Early diagnosis of STB is important to prevent advanced damage and suffering.[7] Wares et al. mention that radiological features of STB are nonspecific.[1] However, in this study, we disclose 7 key radiological findings observed in the STB lesion (Table 1). Imaging is important for diagnosis and treatment of STB, and the diagnostic roles of various imaging modalities have been

discussed in Shikhare's report.[8] MRI and spiral CT are currently the most commonly used imaging methods.

Despite the availability of well-established and effective chemotherapeutic agents against TB, the complications after STB, such as syringomyelia, permanent neurological deficits, and spinal osseous defects, sometimes remain unresolved even after the eradication of the pathogens. Therefore, surgical approaches are indicated for STB to minimize these serious complications. All of the cases treated with ATA in this study showed a good response, barring 1 patient who contracted hepatitis. Three patients received surgical interventions. Treatment of STB, which is a major public health problem, is possible only if it is detected early, and an important prerequisite for detection is the modality used for diagnosis.[1]

STB is one of the important forms of ETB, and this study may be representative of the current demographic features of STB patients in central Taiwan. A high degree of clinical acumen, along with the 2 clinical factors and 7 neuroradiological findings outlined in this study are important for STB diagnosis and for starting treatment with ATAs, which is the current mainstay of treatment.

Conflicts of interest

The authors have none to declare.

Informed consent

Written informed consent was obtained from the patients for publication of this case series and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Authors' contributions

Both CHC and YMC designed and performed this study. CYC, JKH, CWL, and CHC treated the patients described in this study. CHC and YJC analyzed the data regarding the infectious diseases and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the Changhua Christian Hospital for the grant support (104-CCH-IRP-001, 105-CCH-IRP-001). All authors thank the Tuberculosis Case Managers of the Changhua Christian Hospital for their assistance in data collection.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijtb.2016.05.014.

REFERENCES

1. Chen YH, Lin CB, Harnod T, et al. Treatment modalities for tuberculosis of the spine: 22 years' experience in east Taiwan. *Formosan J Surg*. 2013;46:189–194.
2. Haider ALM, Bones and joints tuberculosis. *Bahrain Med Bull*.2007;29:1–9.
3. Centers for Disease Control, Department of Health, ROC (Taiwan). *Taiwan Tuberculosis Control Report 2011*. ROC: Centers for Disease Control, Department of Health, ROC (Taiwan); 2011.
4. Jutte PC, van Loenhout-Rooyackers JH, Borgdorff MW, van Horn JR. Increase of bone and joint tuberculosis in the Netherlands. *J Bone Jt Surg Br*. 2004;86:901–904.
5. Centers for Disease Control, Department of Health, ROC (Taiwan). *Taiwan Guidelines for TB Diagnosis & Treatment*. 5th ed. ROC: Centers for Disease Control, Department of Health, ROC (Taiwan); 2011.
6. Weng CY, Chi CY, Shih PJ, et al. Spinal tuberculosis in non-HIV-infected patients: 10 year experience of a medical center in central Taiwan. *J Microbiol Immunol Infect*. 2010;43: 464–469.
7. Wares F, Balasubramanian R, Mohan A, Sharma SK. Extrapulmonary tuberculosis: management & control. In: Agarwal, Chauhan, eds. In: *Tuberculosis Control in India. Directorate General of Health Services/Ministry of Health and Family Welfare*. India: Elsevier; 2005:95–114.
8. Shikhare SN, Singh DR, Shimpi TR, Peh WC. Tuberculous osteomyelitis and spondylodiscitis. *Semin Musculoskelet Radiol*. 2011;15:446–458.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Radiographic chest findings and immunological status in HIV-positive patients with tuberculosis coinfection in a sub-urban Nigerian tertiary hospital

A.A. Olatunji [a,*], P.O. Olatunji [b], A.A. Salako [c]

[a] Department of Radiology, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria
[b] Department of Haematology and Blood Transfusion Services, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria
[c] Department of Community Medicine and Primary Care, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu, Ogun State, Nigeria

ARTICLE INFO

Article history:
Received 14 April 2015
Accepted 9 July 2015
Available online 15 July 2016

Keywords:
Chest radiograph
HIV/AIDS
Pulmonary TB
CD4 counts

ABSTRACT

Introduction: The study was undertaken to assess chest radiographic features and lymphocyte counts among HIV-positive patients with TB coinfection.
Materials and Method: We reviewed the chest radiographs of all newly diagnosed, treatment-naïve HIV-positive patients attending the Treatment Centre at the Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria. The radiographs were examined for presence or absence of features of tuberculosis and pneumonia. Those with tuberculosis were further evaluated for presence of cavities and milliary appearance. The demographic characteristics of the patients were recorded.
Results: Two hundred and ninety-five radiographs were reviewed, consisting of 192 females, 103 males with mean ages of 33.6 ± 11.65 and 37.85 ± 13.54 years, respectively. Normal radiographs were found in 68.5% patients, features of tuberculosis in 27.8%, and pneumonia in 2.7%. The percentages of males and females with tuberculosis were 35% and 25%, respectively. Patients with milliary TB were from the youngest age group and those with cavities had CD4 cell count below 200 cells/mm^3. Cavities occurred most frequently in the lower zones. WBC and counts were highest in patients with pneumonia.
Conclusion: Normal chest radiographs were associated with mild clinical course. Males were more frequently involved in TB coinfection. Cavities were associated with lowest CD4 cell count and occurred more in lower zones. Patients with HIV/PTB coinfection had the most severe weight loss. There was no statistically significant difference in absolute lymphocyte count between patients with or without tuberculosis. Chest radiograph remains a veritable tool for identifying HIV/AIDS patients with tuberculosis whether sputum is positive or negative.

* *Corresponding author.*
E-mail address: ayodeji.olatunji@yahoo.com (A.A. Olatunji).
http://dx.doi.org/10.1016/j.ijtb.2015.07.003

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a pandemic affecting an estimated 33.4–39.5 million people with about 2 million dying from AIDS-related disease each year.[1] Sub-Saharan Africa has the largest number of HIV-infected subjects worldwide and Nigeria still has the 2nd largest number of people living with HIV/AIDS (PLWH) in Sub-Saharan Africa and the highest in the West African subregion.[2,3] HIV/TB coinfection is a disease of global concern because of its effect on morbidity and mortality.

By the report of WHO, the Africa region accounted for most HIV-positive tuberculosis cases (79%), followed by Southeast Asia region (mainly India), which had 11% of total cases in 2007, although the prevalence of HIV-infection among patients with tuberculosis ranges from 50% to 80% in many settings in sub-Saharan Africa, while in other parts of the world it varies from 2% to 15%.[4]

Human Immunodeficiency Virus (HIV) and Mycobacterium tuberculosis (MTB) have a synergistic interaction, each propagating the progression of the other.[4] Individuals with HIV infection are also at greater risk of Tuberculosis (TB), with an estimated 50–70% of HIV-positive person likely to develop tuberculosis[5] and atypical mycobacterial infection as well as extra pulmonary TB in their lifetime.[6] HIV has contributed to the increase in the global incidence and mortality from tuberculosis. Coinfection with HIV leads to difficulties in both the diagnosis and treatment of tuberculosis and hence increased the risk of treatment failure, relapse,[4] and death.

The chest radiograph is a simple and common procedure performed to evaluate the thoracic organs including the lungs, heart, and the chest wall. This singular procedure has been found to be useful in diagnosing the disease underlying various symptoms such as persistent cough which may be dry or productive, shortness of breath, chest pain, and the presence of fever. This is particularly useful in the light of low sensitivity of sputum test due to immunosuppression (Fig. 1).

The chest radiograph is, therefore, an important diagnostic tool in assessing the complications as well as the manifestations of HIV infection as it concerns the chest. It is accurate for diagnosing common chest complications with reported accuracies of 64%, 75%, and 84% for bacterial pneumonia, PCP, and MTB, respectively, in a blinded trial.[7] It is mandatory for all patients presenting with unexplained pulmonary or constitutional symptoms to have a chest X-ray done, including those with suspected central nervous system tuberculosis, where it may provide additional support for the diagnosis of tuberculosis.[8]

There is considerable overlap in the radiographic findings of the numerous infectious and neoplastic entities that are known to occur with increased frequency in AIDS patients. This degree of radiological variation can create considerable difficulty in the interpretation of chest radiographs.

The current study is aimed at documenting the chest radiographic patterns of patients with HIV/AIDS and tuberculous coinfection as well as examines the possible association of patterns with age, CD4 cell count being one of the markers for evaluating the degree of immunosuppression and HIV disease progression.[9] This may lead to improved diagnosis and help in reducing the diagnostic dilemmas usually related to these diseases and thus improved life expectancy.

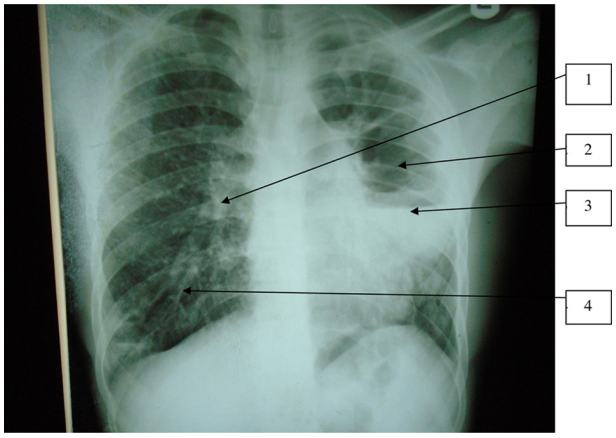


Fig. 1 – Chest radiograph of a HIV patient with TB coinfection showing reticulonodular shadows (1), cavity in Lt mid +Lt Upper zones (2), air fluid level (3), and fibrotic changes (4).

2. Materials and method

The study was carried out at the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria. The patients were recruited from the hospital's CDC-supported facility with a laboratory equipped for HIV diagnosis and CD4 cell count.

A retrospective analysis of the chest radiographs of all newly enrolled, treatment-naive patients attending OLABISI ONABANJO UNIVERISTY TEACHING HOSPITAL IHVN Action site, SAGAMU, OGUN STATE, NIGERIA between FEBRUARY 2008 and DECEMBER 2009 was carried out. A detailed data consisting of age, sex, weight, chest findings, CD4 counts, and total lymphocyte counts and White blood count were extracted both from request cards and case notes.

The details of the radiographic pattern on the chest radiographs of infiltrates (nodular, reticulonudular, patchy, homogeneous or in-homogeneous opacification), pleural effusions, lymph mode enlargement (hilar, mediastinal or axillary, and supraclavicular), cavities (including the anatomic site), upper lobe blood diversion, and the presence or absence of pleural thickness were noted.

Analysis was done on SPSS version 16. Data were displayed on tables and Chi square test was used to determine the significance of radiographic appearance. The effects of radiographic appearance on the discrete variable were determined by the student's t' test.

3. Results

A total of 295 chest radiographs were obtained, made up of 103 males and 192 females who were proven retroviral-positive with a mean age of 35 ± 12.4 years and a range of 6.5–68 years. 202 (68.5%) patients had normal radiographs, 82 (27.8%) had

Table 1 – Age and sex distribution of patients.

TB status	Number of patients		
	Male	Female	Total (%)
TB features	17	19	46(56.1)
TB with cavities	15	16	31(37.8)
Milliary TB	2	3	5(6.1)
Sub-total	34	48	82(100)
TB Negative	64	138	202
Pneumonia	5	6	11
Total	**103**	**192**	**295**

features of tuberculosis, and 11 (3.7%) had pneumonia. Of the patients with TB, 31 (37.8%) and 5(6.1%) had cavitations and milliary form, respectively. Thirty-four (33%) male patients had TB coinfection, as against 48 (25.0%) of female patients. The difference was statistically significant ($p = 0.005$) (Table 1).

The mean age of the male patients was 37.85 years with a standard deviation of 13.54 years, while that of the female patients was 33.60 ± 11.65 years with a range of 0.2–67.5 years. The mean age for all patients was 35.09 ± 12.49 years. No statistical difference in age was recorded between the male and female patients. The mean age of patients without tuberculosis was 36.4 years, while that of those with TB co-infection was 33.6 years. Those with TB cavitation had mean age of 24.4 years, and those with milliary TB had mean age of 16.8 ± 18 years. HIV patients with pneumonia had mean age of 21.4 ± 18 years and were significantly younger ($p < 0.0001$).

Among the male patients, 64 (62.1%) had normal chest radiographs, 34 (34%) had tuberculosis coinfection, and 5 (4.9%) had pneumonia. Among female patients, 138 (91.9%) had normal radiographs, and 48 (25%) had tuberculosis coinfection, while 6 (3.1%) had pneumonia. The proportion of male patients with tuberculosis was significantly higher than female patients ($p = 0.005$). A total of 82 cases had pulmonary tuberculosis in the series. Milliary TB occurred in 5 (6.1%), while pleural effusion occurred in 10 (3.4%) of the 82 patients with TB.

The mean weight of positive retroviral patients who had normal chest radiographs was 57.3 kg ± 14.7, while those who had PTB were 48.4 ± 16 kg. The patients who had pneumonia had a mean weight of 31.2 ± 22.2 kg. This was statistically significant ($p = 0.000$) (Table 2).

The mean CD4 counts for all the patients in the study group are 357.0 ± 317.4 years. The mean CD4 cell count of patients who had pulmonary tuberculosis was 301 ± 363 cells/mm^3, while patients with normal chest radiographs had a CD4 count of 276.6 ± 297.3 cells/mm^3. The mean CD4 count in patients with pneumonia is 357 ± 363. No statistical difference is seen in the CD4 counts ($p = 0.7$).

Patients with cavitations have mean CD4 cell count of 198.4 cells/mm^3 while those with milliary TB had CD4 cell count of 600 ± 881.1 cell/mm^3. Cavities were associated with significantly lower CD4 cell count ($p = 0.021$). The mean CD4 cell count of patients with pneumonia was 438 ± 438.1 cell/mm^3. Patients with pneumonia were significantly younger ($p < 0.0001$). The patients with the normal radiographic findings had a mean age of 36.4 years and a mean CD4 count of 283 ± 295 cell/mm^3 in 83.7% patients (Table 3).

The absolute lymphocyte count of the retroviral positive patients with PTB was 2.2 ± 1.4 × 10^9 L^{-1}, while that of patients with normal chest radiographs was 2.1 ± 0.96 × 10^9 L^{-1}. Patients with pneumonia had absolute lymphocyte count of 4.0 ± 3.2 × 10^9 L^{-1}. The lymphocyte count of patients with pulmonary tuberculosis was significantly lower than that of patients with pneumonia ($p = 0.000$).

In patients with cavitations, cavities were located in the lower zone only in 20.6%, middle zone only in 17.2%, and upper zone only in 13.8% of the cases. The cavities were bilateral in 37.8% of the cases, and occur as 10.3% each in the right upper + left middle zones, right upper + left lower zones. Cavities occurred in the right lower and left lower zone in 6.9% of the cases. Bilateral combinations of cavities in the right middle + left middle, right lower + left upper, and right lower + left lower zones were found in 3.4% each in the patients. Generally, the cavities tended to occur more on the right than the left, although it is not statistically significant (Table 4).

4. Discussion

Tuberculosis remains the commonest opportunistic disease in HIV-positive persons and chest radiograph continues to be

Table 2 – Age and weight of patients according to chest findings in HIV/AIDS patients.

Chest radiograph finding	Age (years)		Weight (kg)	
	Mean ± SD	No. of pts	Mean ± SD	No. of pts
TB features	34.9 ± 13	46	47 ± 11	43
TB with cavities	34.4 ± 11	31	54.3 ± 15	31
Milliary TB	16.8 ± 19	5	25 ± 18	5
Pneumonia	21.4 ± 19	11	31.2 ± 22	22.2
Normal chest	36.4 ± 11	202	57.2 ± 14	200
Total	35.1 ± 13	295	54 ± 15	288
p value	$p = 0.000$		$p = 0.000$	

Table 3 – Effect of radiologic lung findings on CD4 cell count and lymphocyte count.

Chest radiograph finding	Age (years)	CD4 cell count/mm^3		Lymphocyte count (×10^9 L^{-1})	
		Mean	SD	Mean	SD
TB features	39	339	323	2.2	1.4
TB with cavities	29	198	239	1.9	1.0
Milliary TB	5	600	881	4.8	4.4
Pneumonia	11	438	438	4.0	3.2
Normal chest	193	272	289	2.0	1.0
Total	277	285	317	2.2	1.4
p value		$p = 0.024$		$p = 0.000$	

Table 4 – Frequency of cavity positions within the lung fields.

Lung zone	Frequency	%
Upper zone	4	13.8
Middle zone	5	17.2
Lower zone	6	20.7
Rt upper + left upper	2	6.9
Rt. Upper + Lt Mid	3	10.3
Rt. Upper + Lt Lower	3	10.3
Rt. Lower + Lt. Lower	2	6.9
Rt. Mid + Lt. Mid	2	6.9
Rt. Lower + Lt. Lower	1	3.4
Rt. Lower + Lt. Upper	1	3.4
Total	29	100

relevant in evaluation of patient at least in developing countries such as Nigeria. The preponderance of female patient and the mean age of 35.09 years agree with established epidemiology of HIV/AIDS due to greater vulnerability of women and the socio-cultural factors such as polygamy and commercial sex work.[1,7] The mean age reflects the fact the disease affects the sexually active and the productive segment of the population.[2,10–13] Eighty-two (27.8%) out of the 295 patients had radiological features of tuberculosis. This is within the prevalence of 4–44% reported in different populations in literature.[10,14] A significantly higher prevalence of tuberculosis found in male (62.4%) patients than in the females (34%) reflects the same pattern observed in HIV-negative patients.[4,15–19]

Other features of primary and reactive tuberculosis seen in the chest radiographs of the patients reviewed include: pleural effusion (unilateral or bilateral) especially in children, lymph node enlargement, bronchopulmonary dissemination, obvious nodules (solitary or multiple) and fibrosis with cavitations[7,8] which were consistent with previous reports.[7,8] Prominent in this study were cavitations and milliary forms, which were seen in 39 and 5 of the patients, respectively.

It should, however, be noted that absence of chest radiographic features does not exclude the presence of tuberculosis, as normal chest radiographs may be seen in HIV-infected patients, despite active infection due to depressed immunity, which makes it difficult to mount a granulomatous reaction to invading organism.[11] In some studies in other parts of the world, the rate of normal chest radiographs ranges between 6%–11% and 18%–30%.[12] The quality of production of the radiographs, which is an integral part of good radiographic reporting, may also play an important role. Clinicians should, therefore, be cautious since normal chest radiography does not always rule out PTB, thus, indicating the need for other imaging techniques such as lung computerized tomography (CT) scan (where available and affordable) or other laboratory diagnostic techniques.[15,18] It is, however, rare for patients without HIV infection to have normal roentgenograms when infected with TB.[11]

Eleven (3.8%) of the patients who did not have features of tuberculosis had pneumonia. These were relatively younger patients with mean age of 21.4 years. This is not strange, as recurrent pyogenic bacterial pneumonia is one of the most common clinically apparent parenchymal lung infections in the HIV population, both before and after the onset of AIDS. Bacterial pneumonias tend to occur throughout the course of HIV illness, becoming increasingly common with a falling CD4 count. Since they often occur at relatively high CD4 counts, bacterial infections tend to be the first pneumonic process to occur prior to the onset of full-blown AIDS.[8] A CD4 count of 438 cell/mm^3 recorded in this study may, therefore, not be out of place. The bronchopneumonia seen with AIDS can be extensive and bilateral.[8] The typical radiographic appearance of bacterial pneumonia on chest radiographs in AIDS is the same as that in an immune competent host with lobar or segmental consolidation but progressing rapidly, with frequent multilobar or bilateral disease.[20]

The presence of cavities in 37.8% of the patients with HIV-TB coinfection and the high frequency of unilateral lesions in the lower zones, mid zone, and the upper zones of the lungs, and the predilection of bilateral lesions for the right upper + left mid zones and right upper + left lower zones were in agreement with the study of Ghiya et al.[21] and Agizew et al.[22] The radiographic features of reactivation of TB including patchy consolidation, lower lobes cavitation, nodularity, and effusions were also seen in these series of patients.

5. Conclusion

HIV infection most commonly affects the younger economically productive section of the society. It is more common in the females. TB coinfection is more prevalent in the male patients. It occurs more unilaterally on plain chest radiographs with cavities found more frequently in the lower and mid zones. Milliary TB was more frequent in the relatively young patients. Cavities were found in the relatively older age group. Weight loss can be a pointer to the level of reduction of immune status in the retroviral positive patients. The lowest CD4 cell counts and total lymphocytes counts are associated in patients with TB cavitations, while the highest count were associated with those with pneumonia. Patients with cavitations have the highest mean age. Chest radiographs are still useful in the continuous management of HIV cases both in the pre-treatment and post-treatment period, for effective monitoring and follow-up of cases even where modern imaging equipments are readily available.

Conflicts of interest

The authors have none to declare.

Acknowledgements

This publication was supported by Cooperation Agreement Number PS000651-03 from Centre for Disease Control (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

REFERENCES

1. Akinola RA, Balogun TM, Adeniji AA, Onakoya JAA, Fadeyibi IO. Spectrum of chest X-ray findings among human immunodeficiency virus positive individuals in a Nigerian Tertiary Hospital. *SAARC J Tuber Lung Dis HIV/AIDs*. 2013;X (2):27–34.
2. Nyamande K, Lalloo UG, Vawda F. Comparison of plain chest radiography and high resolution CT in human immunodeficiency virus infected patients with community-acquired pneumonia: a sub-Saharan Africa study. *Br J Radiol*. 2007;80:302–306.
3. PM News. *3.1 Million people infected with HIV in Nigeria*. (http://pmnewsnigeriacom/2011/03/25about3.1-million-people-infectedwith-hiv-in-Nigeria-health-minister/).
4. Jaryal A, Raina R, Sarka M, Sharma A. Manifestations of tuberculosis in HIV/AIDS patients and its relationship with CD4 count. *Lung India*. 2011;28(4):263–266. http://dx.doi.org/10.4103/0970-211385687.
5. Allen CM, AL-Jahdali HH, Irion KL, Ghanem S AI, Gouda A, Khan AN. Imaging lung manifestations of HIV/AIDs. *Ann Thorac Med*. 2010;5:201–216.
6. Whiteman M, Espinoza L, Post MJ, Bell MD, Falcone S. Central nervous system tuberculosis in HIV-infected patients: clinical and radiographic findings. *AJNR Am J Neuroradiol*. 1995;16(6):1319–1327.
7. Patel AK, Thakar SJ, Ghanchi FD. Clinical and laboratory profile of patients with TB/HIV co-infection: a case series of 50 patients. *Lung India*. 2011;28(2):93–96. http://dx.doi.org/10.4103/0970-2113.80316.
8. Desalu OO, Olokoba A, Danfulahi M, et al. Impact of immunosuppression on radiographic features of HIV related pulmonary tuberculosis among Nigerians/Nijeryahalkinda ileiliskilibagisikliksistemininbaskilanmasininakoiger tuberkulozununradyolojikbulgularinaetkileri. *Tur Toraks Der*. 2009;10:112–116.
9. Affusim C, Abah V, Kesieme EB, Anyanwu K, Salami TA, Eidediyi R. the effect of low CD4+ lymphocyte count on the radiographic patterns of HIV patients with pulmonary tuberculosis among Nigeria. *Tuberc Res Treat*. 2013;2013:535769. http://dx.doi.org/10.1155/2013/535769.
10. Mir MA, Ahmad PM, Siddeque MA, Sofi FA, Ahmad SN, Dar MR. Clinical and demographic profile of HIV/AIDS patients diagnosed at a tertiary care centre in Kashmir. *J Pak Med Assoc*. 2010;60(6):428–431.

[11]. Jaryal A, Raina R, Sarkar M, Sharma A. Manifestations of tuberculosis in HIV/AIDS patients and its relationship with CD4 count. *Lung India*. 2011;28(4):263–266.

[12]. Hadadi A, Tajik P, Rasoolinejad M, Davoudi S, Mohraz M. Pulmonary Tuberculosis in patients with HIV/AIDS in Iran. *Iran J Public Health*. 2011;40(1):100–106.

[13]. Verma SC, Dhungana GP, Joshi HS, Kunwar HB, Pokhrel AK. Prevalence of pulmonary tuberculosis among HIV infected persons in Pokhara, Nepal. *J Nepal Health Res Counc*. 2012;10 (1):32–36.

[14]. Teo SY, Ona CL. Clinics in diagnostic imaging (108). *Tuberculous dactylities* of thumb, medastinal and left hilar lymphadenopathy, and probable left cervical lymphadenopathy. *Singapore Med J*. 2006;47(3):243–249. quiz 250.

[15]. King LJ, Padley SPG. Imaging of the thorax in AIDS. *Imaging*. 2002;14:60–76.

[16]. Nwobu GO, Okodua MA, Tatfeng. Comparative study of HIV associated pulmonary tuberculosis in chest clinics from two regions of Edo State, Nigeria. *Online J Health Allied Sci*. 2004;3:4.

[17]. Tarbasi P, Mirsaeidi SM, Amiri M, Mansouri SD, Masjedi MR, Velayati AA. Clinical and laboratory profile of patients with tuberculosis/HIV coinfection at a national referral centre: a case series. *East Mediterr Health J*. 2008;14(2):283–291.

[18]. Nissapotorn V, Kuppusamy I, Sim BL, Quek KF, Khairul Anuar A. Tuberculosis in HIV/AIDS patients: a Malaysian experience. *Southeast Asian J Trop Public Health*. 2005;36 (4):946–953.

[19]. Kisembo HN, Boon SD, Davis JL, et al. Chest radiographic findings of pulmonary tuberculosis in severely immunocompromised patients with the human immunodeficiency virus. *Br J Radiol*. 2012;85(1014):El 30–El 39. http://dx.doi.org/10.1259/bjr/70704099.

[20]. Yoo SD, Cattamanchi A, DenBoon S, et al. Clinical significance of normal chest radiograph among HIV-seropositive patients with suspected tuberculosis in Uganda. *Respirology*. 2011;16(5):836–841. http://dx.doi.org/10.1111/j.1440-1843.2011.01981.x.

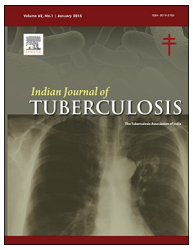
[21]. Ghiya R, Naik E, Casanas B, Izurieta R, Marfatia Y. Clinico-epidemiological profile of HIV/TB coinfected patients in Vadodara, Gujarat. *Indian J Sex Transm Dis*. 2009;30(1):10–15. http://dx.doi.org/10.4103/0253-7184.55472.

[22]. Agizew T, Bachhuber MA, Nyirenda S, et al. Association of chest radiographic abnormalities with tuberculosis disease in symptomatic HIV-infected adults. *Int J Tuberc Lung Dis*. 2010;14(3):324–331.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original Article

Immunotherapy for non-responders among patients of spinal tuberculosis

Ayush Gupta [a], *Ajay Gupta* [b,*], *Awkash Kumar* [b], *Sumit Arora* [b]

[a] *Department of Medicine, L.N. Hospital, New Delhi 110002, India*
[b] *Department of Orthopaedics, Maulana Azad Medical College and Associated L.N. Hospital, New Delhi 110002, India*

ARTICLE INFO

Article history:
Received 26 April 2015
Accepted 13 July 2015
Available online 4 June 2016

Keywords:
Cellular immunity
Influenza
Mycobacteria
Salmonella
Vaccine

ABSTRACT

Background: Combined chemo- and immunotherapy are the major advancement in the treatment of tuberculosis. Immunotherapy supposedly increases cure rate while reducing the duration of treatment and tissue damage. Non-responders are those patients of tuberculosis who do not respond to anti-tubercular therapy (ATT) in the desired manner despite the mycobacteria showing sensitivity to the given drugs. The role of immunotherapy in the treatment of this particular subset of patients has been investigated scarcely.

Methods: The present study included a retrospective review of prospectively collected clinico-radiological data of 14 non-responder patients who were taking ATT for spinal tuberculosis for a mean duration of 10.3 months. An immunotherapeutic regime comprising of single intramuscular injection of vitamin D 600,000 IU, 3 days course of oral albendazole 200 mg daily, salmonella vaccine 0.5 ml intramuscular and influenza vaccine 0.5 ml intramuscular were added to ATT. The vaccines and the course of oral albendazole were repeated after a month.

Results: Before immunotherapy, seven patients were partially dependent while other seven were completely dependent on others for activities of daily living. All except one patient after treatment became independent till last follow-up (p value <0.01). Post immunotherapy, ATT was continued for mean duration of 4.9 months with mean follow-up of 22.4 months. All patients showed good clinical response within 2–6 weeks after the initiation of immunotherapy.

Conclusions: The crux to success of the immunotherapy regime is its potential to restore the existing Th1 Th2 imbalance and to provide substitute to the anergic and dysfunctional immune cells.

1. Introduction

Tuberculosis is an immunological disease with infective transmission. Unlike other microbial infections, which destroy host cells either by direct contact or through release of endotoxins or exotoxins, mycobacteria invokes tissue destruction through inappropriate immune reaction to its antigens. Most efforts to fight against the challenging disease have been directed toward merely killing of the infective pathogen, while

* *Corresponding author at*: DII/315, Pandara Road, New Delhi 110003, India. Tel.: +91 1123073795.
E-mail address: drajaygupta@hotmail.com (A. Gupta).

http://dx.doi.org/10.1016/j.ijtb.2015.07.006

the immune component of the disease, somehow, has never received the attention it deserves. Various immunotherapeutic agents have targeted the existing host anti-tubercular immune response with an aim to either kill the bacilli or contain it. These include (1) antigenic stimulation with BCG or M. vaccae or RUTI vaccinations to augment Th1 response,[1–3] (2) biological therapy to enhance the Th1 protective response with many different cytokines like interleukin 2 and IFN γ etc.,[4,5] and (3) anti-Mycobacterial antibodies.[6] There have been recent reports about immune response modifier like corticosteroids, thalidomide, or anti TNF-α, etc., reducing systemic inflammation.[7–10]

In endemic areas, majority of extrapulmonary and skeletal tuberculosis patients receive ATT on mere clinico-radiological correlation and without any bacteriological or histopathological confirmation. It is not uncommon to see patients who, despite receiving ATT for months or even years, fail to show clinical improvement and rather show signs of worsening. Many of these patients, during the course of their treatment, turn out to be suffering from multidrug-resistant (MDR) tuberculosis. However, a significant number of such patients who have shown to harbor Mycobacteria (Mtb) sensitive to ATT pose a real challenge. These non-responders may form significant number of patients from the endemic areas like Asian sub-continent and have forced many physicians to question efficacy of short-term chemotherapy making all their patients to continue the medication for 18 or even 24 months.

A review of literature showed very scarce attention to such non-responders, which contribute significantly to the quantum of tubercular patients in the developing world. We could find just one study, which used immunotherapy in the form of oral levamisole, intradermal BCG, and intramuscular diphtheria tetanus (DT) vaccine for such non-responders with good results.[11] We evaluated the role of intramuscular salmonella and influenza vaccines, injectable vitamin D, and a course of antihelminthic drugs as an adjunct immunotherapy for the non-responding cases suffering from spinal tuberculosis.

2. Material and methods

This study is a retrospective review of prospectively collected clinico-radiological data of 14 consecutive non-responding cases of spinal tuberculosis who were diagnosed and treated at our government-based, tertiary-level, teaching referral center from 2009 to 2013. The non-responding cases of spinal tuberculosis of >12 years of age of either gender were considered for proposed immunotherapy. The cases with chronic illnesses like uncontrolled diabetes, renal or hepatic disorders, and HIV infection were excluded from the study including patients harboring MDR strains of Mtb. A written informed consent was obtained from all the patients before starting immunotherapy. All patients were broadly divided into three groups on the basis of clinical scenarios: (1) non-responders based on the clinical/hematological/radiological parameters despite sufficient duration of ATT of 6 months or more (6 patients), (2) non-responders with worsening of the disease despite continued ATT for 3 months or more (5 patients), and (3) non-responders despite an added surgical debridement and continued ATT post-operatively for 3 months or more (3 patients).

The patients were initially evaluated with detailed clinical and neurological examinations. The clinical parameters to dictate clinical improvement or deterioration included constitutional symptoms like fever, loss of appetite and loss of weight, local pain, and tenderness, limitation of movements, and change in quantity of discharge or size of abscess, or progression of the neurological deficit if any. The relevant hematological (total and differential leukocyte counts, hemoglobin, and erythrocyte sedimentation rate) and radiological investigations (spine radiographs, chest radiographs, contrast-enhanced magnetic resonance imaging, and computed tomography) were performed on in-patient/out-patient basis. The additional investigations performed were pus for microscopic examination, culture for acid-fast bacilli, polymerase chain reaction (PCR) and nucleic acid amplification test (NAAT), and a work-up for possible drug resistance.

The ATT regimen (category I) included an initial intensive phase consisting of four drugs: Isoniazid (H) 5–10 mg/kg/d; Rifampicin (R) 10–20 mg/kg/d; Pyrazinamide (Z) 25–35 mg/kg/d; and Ethambutol (E) 15–25 mg/kg/d along with Pyridoxine 10 mg for 2 months, three drugs HRE for 3 months, followed by maintenance phase of 4 months of two drugs HR. However, all patients had varied therapeutic profiles both in terms of duration of ATT and even the regimen at the time of start of immunotherapy. Three patients were on category II ATT of five drugs including intramuscular injection of Streptomycin 1 g daily for 90 days, five patients were on repeat intensive phase of four drugs after completing one full category I regimen, four patients were on three drugs phase of category I regime while two patients were on two drugs maintenance phase. The immunotherapy regimen comprised of antihelminthic drug albendazole 200 mg oral once daily for 3 days, single dose intramuscular injection of 6,00,000 IU of vitamin D, intramuscular Salmonella typhi purified Vi-capsular polysaccharide vaccine 0.5 ml (Typbar TCV, Bharat Biotech International Ltd., India), and intramuscular Influenza vaccine 0.5 ml (Influvac, Abbott India Limited, India). The vaccines and the course of albendazole were repeated after a month. All outdoor patients were seen monthly to assess clinical response and early detection of complications (drug-related side-effects, reactivation of disease process, and worsening of neurology). Response to therapy was seen clinically by improvement in back pain, constitutional symptoms, and neurological deficit, biochemically by serial ESR. Radiographs were obtained every 6 weeks.

Statistical analysis: Wilcoxon matched-pairs signed-ranks test was performed, using InStat software for Windows (GraphPad version 3.00, SanDiego, California, USA), to statistically evaluate the significance of clinical outcome. The resulting p value of <0.05 was accepted as statistically significant differences of the median of paired observations.

3. Results

The study included 14 cases with demographic and clinical profile as given in Table 1. The most common presenting symptom was persistent pain in the back (14 patients), fever (8 patients), and weakness of the lower limbs (7 patients). Tenderness (nine patients) and spastic paraplegia/quadriplegia

Table 1 – Patients' table showing demographic details, clinical profile, and follow-up.

No	Age	Sex	Site	Duration of ATT		Clinical details	Diagnostic criterion	MDR-TB	Results	Follow up
				Before im	After imm					
1	25	F	T9-10	6 months	4 months	Pott's spine on ATT for 6 months with no relief. Immunotherapy added.	Clinicoradiological/ Bacteriological	–ve	Improvement in 4 weeks with complete relief in 3 months	24 months
2	21	M	T9-10	7 months	6 months	Developed paraplegia on ATT for 4 months. Antero-lateral decompression showed no neurological recovery till 3 months after the surgery. Immunotherapy added.	Clinicoradiological Bacterio/Histological	–ve	Showing recovery after 3 weeks of immunotherapy.	15 months
3	15	M	T2-9	4 months	4 months	Developed paraparesis despite ATT for 4 months. Immunotherapy added.	Clinicoradiological	Not known	Started recovery in 3 weeks. Complete relief of symptoms in 3 months.	32 months
4	12	F	T10-11	4 months	5 months	Pott's spine with right psoas abscess on ATT for 4 months. Developed paraperesis. Percutaneous pus aspiration done. Immunotherapy added with complete bed rest.	Clinicoradiological/ Bacteriological	–ve	Started showing neurological recovery after 3 weeks of immunotherapy. Complete neural recovery at 6 months.	30 months
5	14	M	T4-10	29 months	4 months	Pott's spine on ATT for 29 months. Worsening with multi-focal tubercular lesions. Immunotherapy added.	Clinicoradiological Bacterio/Histological	–ve	Improvement in 4 weeks. Complete relief of symptoms in 4 months	28 months
6	35	M	T12-L1	12 months	4 months	Pott's spine with left psoas abscess on ATT and repeated pus drainage for 7 months. Streptomycin added for 90 days with no relief. Immunotherapy added.	Clinicoradiological Bacterio/Histological	–ve	Improvement in 4 weeks with complete relief of symptoms in 3 months	28 months
7	41	M	L1-2	15 months	4 months	Pott's spine with left psoas abscess on ATT and repeated pus drainage for 10 months. Streptomycin added for 90 days with no relief. Immunotherapy added after 2 months.	Clinicoradiological Bacterio/Histological	–ve	Improvement in 4 weeks with complete relief of symptoms in 3 months	20 months
8	15	M	C3-5	13 months	12 month	Developed quadriplegia on ATT for 13 months. Skull tong traction applied for 6 weeks and Immunotherapy added.	Clinicoradiological	Not known	Constitutional symptoms improved in 6 weeks. Full neural recovery in 7 months	24 months
9	12	M	T8-9	12 months	6 months	Developed paraplegia on ATT for 9 months. Anterolateral decompression done but showed no recovery till 3 months after the surgery. Immunotherapy added.	Clinicoradiological Bacterio/Histological	–ve	Neurological recovery added in 4 weeks. Recovered to useful activity level at 10 months.	20 months

Table 1 (*Continued*)

No	Age	Sex	Site	Duration of ATT		Clinical details	Diagnostic criterion	MDR-TB	Results	Follow up
				Before im	After imm					
10	14	M	T10-11	10 months	4 months	Pott's spine and left psoas abscess on ATT and repeated pus drainage for 10 months. No relief. Immunotherapy added.	Clinicoradiological Bacteriological	−ve	Improvement in 4 weeks with full relief of symptoms in 4 months.	24 months
11	25	F	L2-3	12 months	4 months	Pott's spine with left psoas abscess on ATT and repeated pus drainage for 5 months. Streptomycin added for 90 days with no relief. Immunotherapy added.	Clinicoradiological Bacteriological	−ve	Showed improvement 3 weeks after immunotherapy. Complete relief of symptoms in 3 months	20 months
12	30	F	L1-3	7 months	4 months	Pott's spine with bilateral psoas abscess on ATT for 7 months. Repeated pus aspiration and drainage with no relief. Immunotherapy added.	Clinicoradiological Bacteriological	−ve	Showed improvement 3 weeks after immunotherapy. Complete relief of symptoms in 3 months	18 months
13	19	M	C4-6, T4-8, L2-4	4 months	4 months	Developed quadriplegia on ATT for 2 months. Skull traction applied. Developed hepatotoxicity. ATT stopped and Immunotherapy added. ATT re-introduced after 12 days	Clinicoradiological	Not known	Improvement in 2 weeks. No worsening despite stoppage of ATT due to hepatotoxicity.	18 months
14	29	F	T6-8	9 months	4 months	Developed paraplegia on ATT. Anterior decompression with instrumentation showed poor neurological recovery. Immunotherapy added 6 months post op.	Clinicoradiological Bacterio/Histological	−ve	Pace of recovery improved within 2 weeks after immunotherapy.	12 months

(seven patients) were the most common clinical findings. Concurrent tubercular infection was noted in four patients: pulmonary tuberculosis (three patients) and tuberculous lymphadenitis (one patient).

Persistence of anterior paraspinal collection was noted in nine patients with psoas abscess in other five patients including one bilateral psoas abscess. All the patients had elevated erythrocyte sedimentation rate (range, 43–105 mm in the first hour). ELISA for HIV was found non-reactive in all the patients. Aspirated pus or surgically evacuated pus/caseous material, curettage from the abscess wall, and infected granulation tissue in 11 patients were submitted for analysis. Acid fast bacilli could be demonstrated in only two patients, whereas positive report for Mtb on PCR or NAAT including sensitivity to drugs or histological evidence of tuberculosis (necrotizing epitheloid granuloma with Langhans' giant cells) was present in all 11 patients. The diagnosis of remaining three patients was based on strong clinico-radiological correlation and the status of MDR could not be established. The mean duration of ATT before and after the initiation of immunotherapy was 10.3 months and 4.9 months. All the patients showed good clinical response in the form of improvement in the neurological status, subsidence of fever or improvement of constitutional symptoms, and reduction in sedimentation rate within 2–6 weeks after the initiation of immunotherapy.

Seven patients were partially dependent and other seven patients were completely dependent on others for daily routine activities and were bed-ridden. Thirteen patients were ambulatory at the time of latest clinical follow-up ($p < 0.01$). One patient remained partially dependent on others for activities. None of the patients in the study group had evidence of recurrence of the disease.

4. Discussion

Tuberculosis may be reactivated or precipitated with reduction in immunity of an individual. Paradoxically, HIV patients with active tuberculosis show worsening of tubercular symptoms with increase in their immunity due to effective antiretroviral drugs and increased CD4 cell counts.[12] The use of immunosuppressant in the treatment of tuberculosis was considered contraindicated, except in some situations like meningitis[7,8] but there are reports demonstrating beneficial effects of immunosuppressant drugs like thalidomide and anti-TNF[10] in reducing tissue destruction due to tuberculosis.

Controversy prevails on the issue of using immunomodulation as an adjunct to ATT.[10,11] It is important to know the immunological etiopathogenesis of the disease in order to understand logics of the immunotherapy. Cellular immunity is mediated by thymus derived (T) lymphocytes, which express a variety of nonpolymorphic function assisted molecules like CD4, CD8, CD28, and CD40. CD4 and CD8 molecules are particularly important, which are expressed on two mutually exclusive subsets of T cells. CD4+ cells can be viewed as a master regulator and these influence the function of virtually all other cells of immune system by secreting soluble cytokines. It comprises of two functionally different subgroup of cells, Th1 and Th2, which are known to cross-regulate each other and have distinct but opposite role to play in etiopathogenesis of tuberculosis. Th1 cells produce INFγ, IL-2, while Th2 cells produce IL-4, IL-5, IL-6, and IL-10. Th1 cells increase antimicrobial activity of macrophages through INF-gamma, whereas Th2 cells support B-cell proliferation and differentiation and hinder Th1 immune response through the production of IL-4.[13,14] As a result, activation of a Th2 response generally leads to disease progression in tuberculosis, whereas activation of a Th1 response leads to protection. It is, therefore, purported that the increased Th2 or decreased Th1 type of cellular immunity may worsen the clinical course of tuberculosis. Role of CD8+ T cells is essentially as cytotoxic cells of tuberculosis-infected targets which function through at least three possible pathways.[15] (1) The CD8+ cells secrete cytokines, but primarily of Th1 type. (2) CD8 T cells lyse mycobacterium-infected macrophages via a Fas granule exocytosis pathway and the Fas–FasL interaction, which results in the apoptotic death of infected target cells, and (3) CD8 T cells have direct antimicrobial activity.

Therefore, the basic principle of immunotherapy is to selectively modulate Th1 or Th2 type of immunity. It may not be unwise to identify and review all such known factors, which have selective effect on Th1 or Th2 type of immunity and to utilize them appropriately in formulating a treatment protocol against the Mycobacterium. Overcrowding, malnutrition, and vitamin D deficiency are known to increase Th2 type of immunity.[16–19] Even the consumption of animal foods like meat and fish is reported to favor Th2 immunity against the diet of vegetarian food.[20] Similarly, parasitic infections, particularly the helminthes, antigens like tetanus toxoid, cholera toxin, etc., are known to induce Th2 immunity.[21–22] Therefore, a course of antihelminthic drugs along with administration of vitamin D was considered a good strategy to downregulate Th2 type of immunity. The other supplementary measures to counter overcrowding and malnutrition, etc., thereby reducing Th2 immunity may also be instituted for better control of the disease.

Although Mycobacterium is reported to be one of the most potent antigenic stimuli for inducing Th1 immunity, other facultative intracellular infections like salmonella, leishmaniasis and various fungal, and viral infections are also known to favor development of Th1 immunity.[23,24] Immunization of mice with recombinant Salmonella strains expressing immunodominant tuberculosis fusion antigen Ag85B-ESAT6 demonstrated reduced numbers of tubercle bacilli in the lungs and spleens throughout the course of infection in comparison to BCG-vaccinated control animals. They concluded that priming with these recombinant Salmonella strains produced increased levels of IFN-γ (over 1250 pg/ml) providing significant added protection against Mtb challenge.[25] Administration of attenuated salmonella vaccine has been reported to reduce allergic response and asthmatic symptoms in murine model.[26,27] Both seem to achieve the said response by generating Th1 cells and CD8+ T cells secreting IFN-γ, which in turn have been shown to inhibit the development of Th2 cells. While salmonella modulates immunity against the mycobacterial infection by maneuvering CD4+ cells,[28] the influenza vaccine achieves it by manipulating CD8+ cells,[27] thus making the two vaccines a perfect combination for the control of mycobacterial infection.

BCG vaccination, which is widely used throughout the world, does not protect against adult pulmonary disease, even though it protects against the more severe forms of childhood TB.[29,30] On the contrary, BCG vaccination, if used as post-exposure vaccine against tuberculosis, is likely to invoke a strong immunogenic response, resulting in exacerbation of the occult disease leading to severe toxicities (Koch's phenomenon).[31] Subcutaneous administration of live or heat-treated BCG to infected mice induced increased antigen-specific T-cell proliferation but did not reduce the bacterial load in the lungs and rather caused larger lung granulomas.[32] Therefore, use of BCG vaccine as a tool of immunomodulation in patients with active tuberculosis appears illogical and is likely to worsen the disease process though some reports have shown otherwise.[11]

Boosting of Th1 type of immunity among non-responders, where great number of Mtb-specific T1 cells are likely to be either dysfunctional or anergic due to persistently elevated antigen doses, can only be accomplished through antigenic stimuli with T1 bias other than Mtb. This view is supported by a study where various DNA vaccines encoding M. leprae Hsp65 or Mtb Hsp70 or ESAT-6 were studied as post-infection treatments in Mtb infected BALB/c mice. It was seen that only the DNA vaccine encoding *M. leprae* Hsp65 resulted in some reduction in bacterial load in the lungs of infected mice.[33] Similarly in another experimental study, after a robust aerosol challenge with pathogenic *M. tuberculosis*, mice immunized with salmonella vaccine were found to have a protective effect of 1.1 log10 CFU reduction in their liver.[25]

Mice coinfected with BCG and influenza A virus exhibited reduced frequency and numbers of CD8 T cells specific to Mycobacterium in the lungs when compared with mice infected with BCG alone. It is due to increasing accumulation of viral specific CD8 T cells into BCG induced granulomas and hence also the increase in local IFN-γ.[34] Tubercular patients after a course of ATT have demonstrated decrease in CD8 cells with switching of their cytolytic function to cytokine production due to the decreased bacterial load.[35] Cytotoxic effector function of CD8 T cells if somehow continues despite sufficient duration of ATT, then may trigger the cytotoxic molecules of these cells such as perforin, granzymes and granulysin to lyse normal host cells, thus pushing these patients to be non-responders. Administration of influenza vaccine substitutes these Mtb specific cytotoxic CD8 T cells with IFN-γ producing influenza specific CD8 T cells, thus causing clinical recovery in such non-responders.[34]

The present study has shortcomings of being a retrospective study and absence of any sophisticated lab parameter to corroborate clinical improvement of the patients. It, therefore, may not be improper to restrict the conclusion to good clinical response after initiation of the proposed immunotherapy to non-responder patients of spinal tuberculosis. Further studies well supported with appropriate immunological and biochemical parameters are warranted to establish and substantiate complete benefit of the treatment modality in a holistic manner. Moreover, the present work due to its excellent and consistent results deserves to be explored regarding its usage to treat other non-responders with extraskeletal tuberculosis as well.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Hoft DF, Kemp EB, Marinaro M, et al. A double-blind, placebo-controlled study of Mycobacterium-specific human immune responses induced by intradermal bacille Calmette-Guerin vaccination. *J Lab Clin Med*. 1999;134:244–252.
2. Mwinga A, Nunn A, Ngwira B, et al. *Mycobacterium vaccae* (SRL172) immunotherapy as an adjunct to standard antituberculosis treatment in HIV-infected adults with pulmonary tuberculosis: a randomized placebo-controlled trial. *Lancet*. 2002;360:1050–1055.
3. Vilaplana C, Gil O, Caceres N, Pinto S, Diaz J, Cardona PJ. Prophylactic effect of a therapeutic vaccine against TB based on fragments of *Mycobacterium tuberculosis*. *PLoS One*. 2011;6:e20404.
4. Johnson JL, Ssekasanvu E, Okwera A, et al. Randomized trial of adjunctive interleukin-2 in adults with pulmonary tuberculosis. *Am J Respir Crit Care Med*. 2003;168:185–191.
5. Dawson R, Condos R, Tse D, et al. Immunomodulation with recombinant interferon-gamma1b in pulmonary tuberculosis. *PLoS One*. 2009;4:e6984.
6. Ballow M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. *J Allergy Clin Immunol*. 2011;127:315–323. quiz 24–5.
7. Kadhiravan T, Deepanjali S. Role of corticosteroids in the treatment of tuberculosis: an evidence-based update. *Indian J Chest Dis Allied Sci*. 2010;52:153–158.
8. Khomenko IS, Chukanov VI, Gergert VI, Utkin VV. Effectiveness of antitubercular chemotherapy combined with corticosteroids and immunomodulators. *Probl Tuberk*. 2010;1:24–28.
9. Corrala LG, Kaplanb G. Immunomodulation by thalidomide and thalidomide analogues. *Ann Rheum Dis*. 1999;58(Suppl 1):I107–I113.
10. Blackmore TK, Manning L, Taylor WJ, Wallis RS. Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes. *Clin Infect Dis*. 2008;47:e83–e85.
11. Arora A, Nadkarni B, Dev G, et al. The use of immunomodulators as an adjunct to antituberculous chemotherapy in nonresponsive patients with osteo-articular tuberculosis. *J Bone Joint Surg*. 2006;8:8-B, 264-9.
12. Wendel KA, Alwood KS, Gachuhi R, Chaisson RE, Bishai WR, Sterling TR. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest*. 2006;120:193–197.
13. Raja A. Immunology of tuberculosis. *Indian J Med Res*. 2006;120:213–232.
14. Surcel HM, Troye-Blomberg M, Paulie S, et al. Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine responses of blood lymphocytes to mycobacterial antigens. *Immunology*. 1994;81:171–176.
15. Cho S, Mehra V, Thoma-Uszynski S, et al. Antimicrobial activity of MHC class I-restricted CD8+ T cells in human tuberculosis. *Proc Natl Acad Sci*. 2000;97:12210–12215.
16. Strachan D P. Allergy and family size: a riddle worth solving. *Clin Exp Allerg*. 1997;27:235–236.
17. González-Torres C, González-Martínez H, Miliar A, et al. Effect of malnutrition on the expression of cytokines involved in Th1 cell differentiation. *Nutrients*. 2013;5:579–593.

18. Neyestani TR, Woodward WD, Hillyer L. Serum levels of Th2-type immunoglobulins are increased in weanling mice subjected to acute wasting protein-energy malnutrition. *Iran J Allergy Asthma Immunol*. 2004;3:1–6.
19. Salahuddin N, Ali F, Hasan Z, Rao N, Aqeel M, Mahmood F. Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study (Supplementary Cholecalciferol in recovery from tuberculosis). A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. *BMC Infect Dis*. 2013;19:22. http://dx.doi.org/10.1186/1471-2334-13-22.
20. Petursdottir DH, Hardardottir I. Dietary fish oil decreases secretion of T helper (Th) 1-type cytokines by a direct effect on murine splenic T cells but enhances secretion of a Th2-type cytokine by an effect on accessory cells. *Br J Nutr*. 2009;101:1040–1046.
21. Elias D, Mengistu G, Akuffo H, Britton S. Are intestinal helminths risk factors for developing active tuberculosis? *Trop Med Int Health*. 2006;11:551–558.
22. Xu-Amano J, Kiyono H, Jackson RJ, et al. Helper T cell subsets for immunoglobulin A responses: oral inmaunization with tetanus toxoid and cholera Tc∼n as adjuvant selectively induces Th2 cells in mucosa associated tissues. *J Exp Med*. 1993;17:1309–1320.
23. Bretscher PA. An hypothesis to explain why cell-mediated immunity alone can contain infections by certain intracellular parasites and how immune class regulation of the response can be subverted. *Immunol Cell Biol*. 1992;70:343–351.
24. Collins FM. Cellular antimicrobial immunity. *Crit Rev Microbiol*. 1979;7:27–91.
25. Lindsay Jennifer Hall. *Phenotypic and Functional Characterisation of Innate and Adaptive Immune Responses after Mucosal Vaccination*. dissertation submitted for the degree of Doctor of Philosophy to Sidney Sussex College. University of Cambridge; 2007. 229 p..
26. Wu CJ, Chen LC, Kuo ML. Attenuated *Salmonella typhimurium* reduces ovalbumin-induced airway inflammation and T-helper type 2 responses in mice. *Clin Exp Immunol*. 2006;145:116–122.
27. Wohlleben G, Muller J, Tatsch U, et al. Influenza A virus infection inhibits the efficient recruitment of Th2 Cells into the airways and the development of airway eosinophilia. *J Immunol*. 2003;170:4601–4611.
28. Ertelt JM, Johanns TM, Mysz MA, et al. Selective culling of high avidity antigen-specific CD4+ T cells after virulent Salmonella infection. *Immunology*. 2011;134:487–497.
29. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberc Lung Dis*. 2001;5:717–723.
30. Rodrigues LC, Pereira SM, Cunha SS, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet*. 2005;366:1290–1295.
31. Iseman MD. *A Physician's Guide to Tuberculosis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.
32. Moreira AL, Tsenova L, Aman MH, et al. Mycobacterial antigens exacerbate disease manifestations in *Mycobacterium tuberculosis*-infected mice. *Infect Immun*. 2002;70:2100–2107.
33. Lowrie DB, Tascon RE, Bonato VLD, et al. Therapy of tuberculosis in mice by DNA vaccination. *Nature*. 1999;400:269–271.
34. Florido M, Grima MA, Gillis CM, et al. Influenza A virus infection impairs Mycobacteria-specific T cell responses and Mycobacterial clearance in the lung during pulmonary coinfection. *J Immunol*. 2013;191:. http://dx.doi.org/10.4049/jimmunol.1202824.
35. Nyendak MR, Park B, Null MD, et al. *Mycobacterium tuberculosis* specific CD8(+) T cells rapidly decline with anti tuberculosis treatment. *PLoS One*. 2013;8:e81564. http://dx.doi.org/10.1371/journal.pone.0081564.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Patients' perceptions about the implementation of Revised National Tuberculosis Control Programme of India

S.K. Verma *, *Karthik Nagaraju*, *Surya Kant*, *R.A.S. Kushwaha*, *S. Kumar*, *R. Garg*

Department of Pulmonary Medicine, King George's Medical University, Chowk, Lucknow, UP, India

ARTICLE INFO

Article history:
Received 9 March 2015
Accepted 1 June 2015
Available online 4 June 2016

Keywords:
Views
Satisfaction
Treatment
Tuberculosis

ABSTRACT

Introduction: Revised National Tuberculosis Control Programme (RNTCP) was launched by the Government of India in 1993. The present study has attempted to analyze the perceptions of patients regarding the implementation of RNTCP.

Materials and methods: The present study was done in a teaching hospital in North India. All patients attending the hospital between March 2014 and July 2014 were included. The study design was cross-sectional using a pre-designed and tested questionnaire. The patients were questioned by personal interviews after obtaining an informed verbal consent.

Results: 74.5% patients were not aware about the kind of disease they were suffering from. 80% patients said that they were not talked in detail about their disease. 64.79% patients said that their doctor was the source of knowledge regarding DOTS prior to treatment. Despite an average distance of 4.75 km between their home and DOTS centre, 90.5% patients said that they did not have any problem in travelling to the DOTS centre for medications. 91.5% and 93.5% patients felt the DOT provider behaviour was supportive and satisfactory respectively.

Conclusion: 64% patients said that they were completely satisfied with the treatment under DOTS, 28.5% were partially satisfied and 7.5% were not satisfied with the treatment.

1. Introduction

India accounts for >25% cases of tuberculosis worldwide with the highest TB burden country in the world and >1000 deaths every day.[1] The Revised National Tuberculosis Control Programme of India (RNTCP) is an application of the WHO-recommended Directly Observed Treatment, Short-course (DOTS) – a comprehensive public health strategy to control tuberculosis.[2]

A variety of factors, such as adherence, compliance and patient satisfaction, are important but usually under studied indicators of effective programme implementation. Utilization of health services, complying with medical treatment and continuing with health care provider, has been found to be more likely among satisfied patients.[3] Feedback from the

* *Corresponding author at*: Department of Pulmonary Medicine, KGMU, Chowk, Lucknow 226016, UP, India. Tel.: +91 9415783700.
E-mail address: drskverma@rediffmail.com (S.K. Verma).

http://dx.doi.org/10.1016/j.ijtb.2015.06.002
0019-5707/

patients regarding the treatment and medical care that they have received ensures that the local health services meet the patients' needs and improved quality of care.[4] The present study has attempted to analyze the perceptions of patients regarding the implementation of RNTCP in India.

2. Materials and methods

The present study was done in a teaching hospital in North India. All patients attending the hospital between March 2014 and July 2014 were included. The study design was cross-sectional in nature and was done using a pre-designed and tested questionnaire. The patients were questioned by personal interviews after obtaining an informed verbal consent.

3. Results

A total of 200 patients attended the hospital during the study period. 53% (n = 106) belonged to the age group between 21 and 40 years, with majority of them being between 21 and 30 years. 63.5% patients (n = 127) were males and 36.5% (n = 73) females. Most of the patients (65%) were literate (capable of reading and writing). Most of the patients in the study were under CAT II DOTS (68%) as compared to CAT I (18%) and CAT IV (14%). Results from the study are presented in Tables 1–6.

4. Discussion

Our study revealed that majority of the patients undergoing treatment with DOTS were males. Multiple studies also showed similar findings.[5,6] Majority of the patients (65%) were literate. Literacy status was found to have a significant influence on awareness about TB in a study by Das P et al.[7]

Table 1 – Knowledge and awareness about TB and DOTS.

	Reponses (n = 200)	Percentage
1a. What did your physician tell you about your disease?		
Something	59	29.5%
Nothing	131	65.5%
Everything	10	5.0%
1b. Awareness about the kind of TB		
Yes	51	25.5%
No	149	74.5%
1c. Anybody talked in detail about TB?		
Yes	40	20%
No	160	80%
1d. Aware about DOTS?		
Yes	71	35.5%
No	129	64.5%
1e. Source of knowledge? (n = 71)		
Advertisement	10	14.08%
Doctors	46	64.79%
Friends and relatives	12	16.90%
Other patients	3	4.23%
1f. Who advised to contact DOTS?		
Came by self	13	6.5%
Doctor	142	71%
Other patients	7	3.5%
Friends and relatives	38	19%

Table 2 – Perception about DOTS centre.

	Reponses (n = 200)	Percentage
2a. DOTS centre opening on time?		
Yes	190	95%
No	10	5%
2b. DOTS centre opened on holidays?		
Yes	35	17.5%
No	165	82.5%
2c. DOTS centre cleaned regularly?		
Yes	182	91%
No	18	9%
2d. Does DOTS centre have adequate staff?		
Yes	190	95%
No	10	5%
2e. Distance from DOTS centre?		
<1 km	39	19.5%
1–5 km	90	45%
5–10 km	40	20%
>10 km	31	15.5%
2f. Do you have any problem in coming to DOTS centre?		
Yes	19	9.5%
No	181	90.5%

Table 3 – Perception about DOTS provider.

	Reponses (n = 200)	Percentage
3a. DOTS centre staff supportive?		
Yes	183	91.5%
No	17	8.5%
3b. Has the DOT provider ever misbehaved or rashly behaved with you or others?		
Yes	13	6.5%
No	187	93.5%

4.1. *Knowledge and awareness about TB and DOTS*

Majority of the patients (80%) felt that the physician or the health worker did not talk to them in detail about TB. Likewise, 65.5% of the patients responded that nothing about their disease was told to them by their physician. However, 29.5% patients responded that they were told at least something by their physician and only 5% said that they were told everything about their disease. This was in contrast to the study by Gupta et al.,[8] where they found that 69.2% patients were explained about their disease and only about 8% were explained about the measures to prevent spread of the disease. Explanation about the disease and measures to prevent spread plays a major role in achieving satisfaction and adherence to treatment. We also found that nearly 74.5% patients were not even aware about their disease status and only 25.5% patients were completely aware about their disease. This was in contrast to the study by Sakalle et al., where they found that nearly 62% patients were aware about tuberculosis.[9] The study by Sakalle et al. was among patients attending the urban health centre of a medical college which explains why most of the patients were informed about their disease. Our study was not restricted to any DOTS centre and the different finding could probably be due to the inadequate explanation about the disease and treatment in the

Table 4 – Perception about diagnosis and follow up.

	Reponses (*n* = 200)	Percentage
4a. Issued ID card?		
Yes	158	79%
No	42	21%
4b. Sputum tested?		
Yes	196	98%
No	4	2%
4c. Charged money for sputum? (*n* = 196)		
Yes	14	7%
No	182	93%
4d. Chest X-ray taken?		
Yes	159	79.5%
No	41	20.5%
4e. Charged money for chest X-ray?		
Yes	59	37.1%
No	100	62.9%
4f. Screened for HIV/AIDS?		
Yes	85	42.5%
No	115	57.5%
4g. How frequently was your weight measured?		
Occasionally	143	71.5%
Never	19	9.5%
Every visit	38	19%
4h. Frequency of visits during IP?		
3 times weekly	169	84.5%
Once weekly	29	14.5%
Once for the whole course	2	1%
4i. Frequency of visits during CP?[a] (*n* = 187)		
Once weekly	55	29.41%
3 times weekly	126	67.38%
Once for the whole course	6	3.21%
4j. Regular diet advice?		
Yes	142	71%
No	58	29%

[a] 187 patients in continuation phase.

Table 5 – Perception about medications from DOTS centre.

	Reponses (*n* = 200)	Percentage
5a. Medicines available at all times?		
Yes	188	94%
No	12	6%
5b. Who was the medicine given to?		
Directly to patient	184	92%
Attendant	16	8%
5c. Medicines given in packs or in open?		
Packs	200	100%
Open	0	0%
5d. Asked to return empty blister packs?		
Yes	162	81%
No	38	19%
5e. Prescribed or forced to buy medicines from outside?		
Yes	16	8%
No	184	92%
5f. Injections available at all times in DOTS centre[a] (*n* = 164)		
Yes	160	97.5%
No	4	2.5%
5g. Where were the injections administered?[a] (*n* = 164)		
DOTS centre	118	71.96%
Elsewhere	46	28.04%
5h. Informed about side effects of the medications?		
Yes	49	24.5%
No	151	75.5%
5i. Any problem in taking medications?		
Yes	9	4.5%
No	191	95.5%
5j. Missed any dose?		
Yes	31	15.5%
No	169	84.5%

[a] 164 patients under CAT II and CAT IV hence requiring injectables.

Table 6 – Overall perception.

	Reponses (*n* = 200)	Percentage
6a. Do you feel that TB can be fully cured?		
Yes	185	92.5%
No	15	7.5%
6b. Overall satisfaction		
Satisfactory	128	64%
Not satisfied	15	7.5%
Partially satisfied	57	28.5%
6c. Recommend treatment to others?		
Yes	187	93.5%
No	13	6.5%

peripheral DOTS centres. Two other studies showed that there was a lack in counselling and explanation about tuberculosis to the patients.[10,11] Only 35.5% patients said that they had heard about DOTS and DOTS centre before starting treatment. The majority (64.5%) were not even aware prior to this therapy. Pinto LM et al. found that only 15% of private TB patients were even aware of the government using a strategy called DOTS in the fight to control TB in India.[12] Another study found the knowledge of the people concerning tuberculosis and DOTS to be grossly lacking.[13] 46 patients gained knowledge about DOTS through their doctor, 12 patients through friends and relatives and 10 patients through advertisements. This is a healthy indication that doctors in general have faith in RNTCP-based DOTS. However, advertisement as a means of spread of knowledge has shown little results. 71% patients responded that it was their treating physician who advised them to contact DOTS centre for treatment. 19% said they started DOTS after advice of their friends and relatives. 6.5% came by themselves and 3.5% were referred by other patients.

4.2. *Perception about DOTS centre*

According to Nezenega et al., waiting time and cleanliness is an independent indicator of adherence and satisfaction towards treatment.[14] In our study, 95% replied that DOTS centre is opened daily at proper time and 91% felt that the DOTS centre was cleaned regularly, which was similar to a study by Portela et al.[15] 95% patients in our study felt that DOTS centre staff were adequate and regularly available, whereas Gupta et al. reported it to be 79.3%.[8] Distance of home or workplace from DOTS centre is an important predictor of satisfaction. Increased distance has been found to be associated with decreased levels of satisfaction. 80.5% patients lived more than 1 km from DOTS centre in our study. In other studies, 6% and 17% patients were living more than 1 km from DOTS centre.[8,16] This large disparity may be due to inability of the patients to correctly assess the distance. In spite of this distance, 90.5% patients in our study said that they did not

have any problem in coming to the DOTS centre. A study found that 10% patients found it inconvenient to come for treatment under RNTCP and thus had to go to a private practitioner.[17] This may be due to the free provision of medications under DOTS which makes the patient come to the DOTS centre for treatment despite the long distances to travel.

4.3. *Perception about DOT provider*

A good patient–DOT provider relationship indicates better patient satisfaction and adherence to DOTS. Majority of the patients (91.5%) felt the staff to be supportive and 93.5% said that the DOTS centre staff did not misbehave with them or with other patients. Similar findings were noted by studies in Ethiopia[14] and New York.[18]

4.4. *Perception about diagnosis and follow-up*

As per norms, every patient is issued an ID card of RNTCP and he/she is followed up. Every visit and every dose administered is noted, including date of start of treatment, change to Continuation Phase, sputum status and date of completion of treatment. 21% patients were not issued an ID card. Sputum microscopy is the chief diagnostic tool under RNTCP.[19] Almost all patients (98%) said that their sputum was tested for AFB (Acid Fast Bacilli) both prior to and during the course of treatment. The remaining patients were diagnosed as extra pulmonary tuberculosis. Treatment services are provided free of charge under RNTCP to patients during both diagnosis and follow-up. 7% and 6.5% patients claimed that money was charged for sputum smear examination and distribution of medicines respectively. Chest X-ray as a diagnostic tool has greater sensitivity but lesser specificity and, hence, its role in the diagnosis of TB is only supportive.[19] 79.5% patients said that chest X-ray was done prior to starting treatment. This shows that still there is a lot of dependence on chest X-ray in diagnosis of tuberculosis. Majority of the patients (57.5%) said that they were not screened for HIV/AIDS after diagnosis of tuberculosis was made. This goes against the recommendation by RNTCP that every patient diagnosed with TB should be encouraged and referred to the nearest ICTC centre to diagnosis.[19] However, screening for HIV/AIDS is voluntary and not mandatory, which probably explains why these many patients were not screened. Regular weight measurement is an indicator of follow-up and also ensures patient interest in the treatment programme. Weight gain is an indicator of good outcome of treatment.[20] 9.5% patients said that their weight was never measured. DOT (Directly Observed Treatment) regime depends on effective implementation of taking medications directly under the observation of a DOT provider. 84.5% and 67.3% patients responded that they visited DOTS centre regularly for treatment during intensive and continuation phases respectively. 51% patients in the study by Davidson et al.[18] said that they felt comfortable while taking medications under observation of the treatment provider.

4.5. *Perception about medications from DOTS centre*

Uninterrupted drug supply is one of the 5 strategies of DOTS therapy. Ensuring its supply in turn ensures better compliance and patient satisfaction.[21] 188 out of 200 patients felt that the medicines under RNTCP were available all the time at DOTS centre. 97.5% said that injectables were available at all times at the DOTS centre. One of the means of checking adherence is to check the empty blister packs at the end of one week during the continuation phase of treatment. Empty blister packs are to be preserved at the DOTS centre.[21] 81% of the patients in the study claimed that they were asked to return the empty blister packs after consumption. A total of 164 patients were under treatment with CAT II and CAT IV, hence requiring injectables. Out of these, the majority (71.96%) said that the injections were administered at the DOTS centre itself. However, the remaining (28.04%) said that they had them administered elsewhere. Under the RNTCP programme, it is advised to get the injectables administered directly from the DOTS centre. When asked whether anyone from the DOTS centre prescribe or force patients to buy medications from outside, nearly 92% patients responded no. The remaining 8% said otherwise, probably because of a short-term lapse in the availability of medications under DOTS.

Initial counselling by the health personnel explaining the treatment plan before starting of the treatment, periodic motivation of patients and prompt action to tackle any problem will enhance compliance. Adequate health education and information about tuberculosis have been demonstrated to be most effective when given as one-to-one counselling. 75.5% patients were not explained about the possible side effects. Ensuring compliance is the main objective of DOTS. 84.5% patients responded that they have not missed any dose of treatment. A similar finding was noted in another study.[8] DOT is a supportive mechanism that ensures the best possible results in treatment of TB. It is neither possible to predict who these patients will be nor is it possible to prevent non-adherence through health education. Studies have shown that there will be poor treatment outcome and high death rates in the absence of DOT, even when regular supply of drugs is ensured. Hence, by providing DOT, RNTCP ensures that patients receive the right drugs, in the right doses, at the right intervals and for the right duration.[19]

4.6. *Overall perception*

92.5% patients felt that TB can be fully cured. 64% patients felt that their treatment under DOTS was satisfactory and 28.5% patients felt that they were only partially satisfied. Remaining 7.5% patients said they were not at all satisfied with their treatment. Similar results were also obtained in another study.[8] 93.5% said that they would recommend this treatment to other patients. This is a healthy finding indicating the faith patients have in the programme and hence better spread of knowledge regarding treatment.

5. Conclusion

We conclude that knowledge of the patients about tuberculosis and the available treatment of DOTS is found to be inadequate. Perception about the DOTS centre and DOT provider is good among most of the patients. Although patients have to travel a fair distance to get medications, they did not have any trouble in

coming frequently. Patients were not explained about the side effects in majority of the centres. Diagnosis, follow-up and treatment have been found to be adequate. Patient's overall satisfaction and trust seem to be adequate. One shortcoming from the study is that the study population was small. Further studies regarding satisfaction and assessment of DOT programme and its implementation are warranted.

Conflicts of interest

The authors have none to declare.

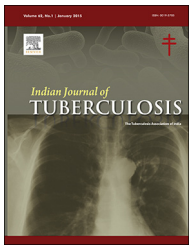
REFERENCES

1. World Health Organization (WHO). *Global tuberculosis report 2013*. Geneva: WHO; 2013. Available from URL: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf (23 October).
2. *Framework for effective tuberculosis control*. Geneva, Switzerland: World Health Organization; 1994[WHO/TB/94.179].
3. Larsen DE, Rootman R. Physician's role performance and patient satisfaction. *Soc Sci Med*. 1976;10:29–32.
4. Health Care Commission-North West London Hospitals NHS Trust: Outpatient survey report. 2004/2005.
5. Karanjekar VD, Lokare PO, Gaikwad AV, Doibale MK, Gujrathi VV, Kulkarni AP. Treatment outcome and follow-up of tuberculosis patients put on directly observed treatment short-course under Rural Health Training Center, Paithan, Aurangabad in India. *Ann Med Health Sci Res*. 2014;4:222–226.
6. Verma SK, Kant S, Kumar S, Prasad R. A five-year follow-up study of revised national Tuberculosis Control Programme of India, Lucknow. *Indian J Chest Dis Allied Sci*. 2008;50:195–198.
7. Das P, Basu M, Dutta S, Das D. Perception of tuberculosis among general patients of tertiary care hospitals of Bengal. *Lung India*. 2012;29:319.
8. Gupta S, Singh JV, Bhatnagar M, Bajpai SK, Garg SK, Chopra H. A study of patient satisfaction towards RNTCP in Meerut district, Uttar Pradesh. *NTI Bull*. 2006;42(Part 1, 2):9–11.
9. Sakalle S, Waskel B, Dixit S, Pandey D, Sirohi S, Saroshe S. A study on patient compliance of tuberculosis enrolled under Revised National Tuberculosis Control Programme. *Natl J Community Med*. 2014;5:96–99.
10. Finlay A, Lancaster J, Holtz TH, Weyer K, Miranda A, van der Walt M. Patient and provider-level risk factors associated with default from TB treatment, South Africa, 2002: A case control study. *BMC Public Health*. 2012;12:56.
11. Sardar P, Jha A, Roy D, Roy S, Guha P, Bandyopadhyay D. Intensive phase non-compliance to anti-tubercular treatment in patients with HIV-TB co-infection: a hospital-based cross sectional study. *J Community Health*. 2010;35:471–478.
12. Pinto LM, Udwadia ZF. Private patient perceptions about a public programme; what do private Indian tuberculosis patients really feel about directly observed treatment? *BMC Public Health*. 2010;10:357.
13. Sharma N. The impact of an IEC campaign on tuberculosis awareness and health seeking behaviour in Delhi, India. *Int J Tuberc Lung Dis*. 2005;9:1259–1265.
14. Nezenega ZS, Gacho Y, Tafere TE. Patient satisfaction on tuberculosis treatment service and adherence to treatment in public health facilities of Sidama zone, South Ethiopia. *BMC Health Serv Res*. 2013;13:110.
15. Portela MC, Lima SML, Brito C, Ferreira VMB, Escosteguy CC, de Vasconcellos MTL. Tuberculosis Control Program and patient satisfaction, Rio de Janeiro, Brazil. *Rev Saúde Pública*. 2014;48:497–507. http://dx.doi.org/10.1590/S0034-8910.2014048004793.
16. Haque MA, Kumar D, Vyas S. A study on socio-demographic profile and feasibility of DOTS provider registered under RNTCP in Varanasi district, Uttar Pradesh. *Indian J Community Health*. 2014;26:107–110.
17. Jaggarajamma K, Balambal R, Muniyandi M, et al. Perceptions of tuberculosis patients about private providers before and after implementation of RNTCP. *Indian J Tuberc*. 2009;56(October):185–190.
18. Davidson H, Smirnoff M, Klein SJ, Burdick E. Patient satisfaction with care at directly observed therapy programs for tuberculosis in New York City. *Am J Public Health*. 1999;89:1567–1570.
19. *Revised National Tuberculosis Control Programme – Training Module For Medical Practitioners*. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2010.
20. Vasantha M, Gopi PG, Subramani R. Survival of tuberculosis patients treated under DOTS in a rural TU, South India. *IJT*. 2008;55:64–69.
21. *Revised National Tuberculosis Control Programme – Module for MPW's and other DOT providers*. New Delhi, India: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2005.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original Article

Epidemiological features of skeletal tuberculosis at an urban district tuberculosis centre

Rajat Chopra [a,*], *Rama Bhatt* [b], *S.K. Biswas* [c], *R. Bhalla* [d]

[a] *Consultant Orthopaedics, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110060, India*
[b] *District Tuberculosis Officer, Ramakrishna Mission Free TB Clinic, 1 Arya Samaj Road, Karol Bagh, New Delhi 110 005, India*
[c] *Senior Chest and TB Specialist, Ramakrishna Mission Free TB Clinic, 1 Arya Samaj Road, Karol Bagh, New Delhi 110 005, India*
[d] *Senior Consultant Orthopaedic Surgeon, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110 060, India*

ARTICLE INFO

Article history:
Received 5 January 2015
Accepted 13 July 2015
Available online 4 June 2016

Keywords:
Skeletal tuberculosis
Extra-pulmonary tuberculosis
Epidemiology

ABSTRACT

Skeletal tuberculosis is an important component of extra-pulmonary tuberculosis. It can lead to substantial morbidity and poses serious occupational and economic problem. We conducted a study in an urban District Tuberculosis Centre (DTC) to assess the burden and distribution of skeletal tuberculosis in the community.

Our centre was catering to a population of 6–7 lakhs between 2007 and 2012. During this period, we treated 11,274 cases of tuberculosis. Out of these, 3086 (27.3%) were cases of extrapulmonary tuberculosis and 219 (1.94%) were cases of skeletal tuberculosis.

Skeletal TB predominantly affects the young Indian population with incidence peaking in the second and third decades of life. 172 patients (78.5%) in our study were new cases. There were no drugs resistant (DRTB) skeletal TB cases till we concluded our study. Tuberculosis commonly involves joints more than long bones. The spinal column was the most commonly involved skeletal site affecting 62.6% of all cases.

The rate of spinal TB in our study is much higher than that reported in literature. The high number of patients calls for close co-ordination between managing orthopaedic surgeons, treating physicians and DOT providers to ensure adequate patient care.

1. Introduction

Continued close monitoring of the epidemiological profile of tuberculosis is essential for the successful implementation of the Revised National Tuberculosis Control Programme (RNTCP). In the early years of RNTCP, 10–15% of all TB cases were estimated to be due to extrapulmonary TB (EPTB).[1] Though this figure has remained steady over the last couple of years (2011 – 15.2%; 2013 – 14.9%),[2,3] there are significant regional variations across the country. Thus, in Delhi, 32.8% of all cases of TB in 2011 were reported to be EPTB cases and the same increased to 35.4% in 2013.[2,3] These assume greater significance in the context of HIV co-infection[4,5] and drug resistant TB (DRTB).

* *Corresponding author*. Tel.: +91 8826178877.
E-mail address: choprarajat@hotmail.com (R. Chopra).

http://dx.doi.org/10.1016/j.ijtb.2015.07.008

Table 1 – Year-wise distribution of TB patients put on DOTS at RKM Free TB Clinic.

Year	Total population covered by RK Mission TB Clinic	Total number of TB patients put on DOTS	Total number of EPTB patients put on DOTS	Total number of skeletal TB patients
2007	600,000	2018	593	40
2008	600,000	1937	633	47
2009	600,000	1824	518	37
2010	600,000	1878	451	33
2011	600,000	1784	369	28
2012	700,000	1833	522	34
Total		11,274	3086	219

Unlike pulmonary TB, which is diagnosed using sputum tests, EPTB cases are mainly diagnosed by imaging techniques such as radiographs, CT scans and MRI scans. EPTB cases present special diagnostic and therapeutic challenges in community settings. Skeletal TB forms an important subset of the total extra-pulmonary TB burden. EPTB cases constitute 11% and skeletal TB constitutes 2% of all TB cases according to a study conducted by the Tuberculosis Research Centre (TRC), Chennai.[6] Although these numbers are not very large per se, skeletal TB can lead to substantial morbidity and poses serious occupational and socio-economic problems through disabilities caused by delays in diagnosis and treatment. This is especially significant with spinal TB, which is reported to constitute 40% of all skeletal TB cases.[6] Spinal TB is not only considered a serious form of TB requiring longer therapy but can also result in serious neurological sequelae if not handled competently. It is therefore important to revisit the burden and distribution of skeletal TB in the community, an exercise that to our knowledge has not been carried out in recent times.

2. Objective

To study the epidemiological features of skeletal tuberculosis at an urban District Tuberculosis Centre (DTC), covered by RNTCP through Directly Observed Therapy Short Course (DOTS).

3. Methodology

We conducted a six-year review of the epidemiological features of skeletal tuberculosis treated at Ramakrishna Mission Free TB Clinic, an urban District TB Centre (DTC) catering to a population of 6–7 lakh in New Delhi. Ramakrishna Mission Free TB Clinic has served as a District TB Centre in the Karol Bagh region of Central Delhi right from the inception of RNTCP in 1998. Starting with a service population of approx. 5 lakh in 1998 it was catering to a 7 lakh population through 18 DOTS centres and 7 Designated Microscopy Centres (DMCs) in 2012. Most of these centres are situated in dispensaries of Delhi government and Central Government Health Services (CGHS).

The electronic registry of TB patients (e-TBPMS, electronic TB Programme Management System) and RNTCP manual TB registers maintained at the Ramakrishna Mission Free TB Clinic were used to obtain a list of all patients who were noted to have "Skeletal/Bone TB" in the TB register between January 2007 and December 2012, a six-year period. The registry as well as the manual record cards of these patients, was reviewed to obtain data regarding demographic profile, site of lesions and other related data.

The majority of cases in this study were diagnosed by orthopaedicians at several government hospitals and medical colleges in Delhi and were referred to Ramakrishna Mission Free TB Clinic for DOTS treatment as they were residents of the Clinic's area of service. Other patients were also routinely referred to orthopaedic consultants for confirmation of diagnosis. The diagnoses were made by the orthopaedicians concerned largely on clinical and radiological grounds with microbiological and histopathological confirmation wherever feasible.

4. Results

From 2007 to 2012, Ramakrishna Mission Free TB Clinic treated 11,274 TB patients in an area having a population of 6–7 lakhs. Out of these, 3086 (27.3%) were cases of extra-pulmonary tuberculosis (EPTB) and 219 (1.94%) were cases of skeletal tuberculosis (Table 1).

4.1. *Gender and age distribution*

There were 102 male and 117 female patients with skeletal TB in the study. 87% of the patients were within 40 years of age and 66% in the 11–30 years age group (Fig. 1).

4.2. *Skeletal involvement in tuberculosis*

The spine was the most common site of skeletal tuberculosis with 62.6% having spinal involvement in one form or

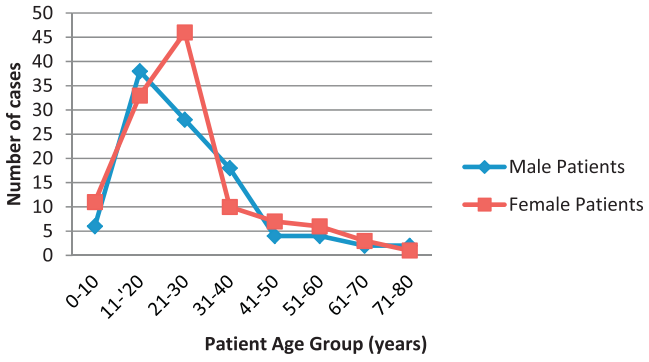


Fig. 1 – Age distribution of skeletal TB patients (2007–2012) by gender.

Table 2 – Distribution of skeletal TB lesions by site.

Skeletal site	Frequency of skeletal site involvement		
	Isolated site involvement	Involvement as part of multiple sites	Total number of sites (%)
Spine	118	19	137 (62.56)
Hip (Hip joint, Ilium, Ischium)	11	1	12 (5.48)
Leg/Thigh (Femur, Tibia, Fibula)	2	1	3 (1.37)
Arm (Humerus, Radius, Ulna, Forearm and Upper Arm)	5	0	5 (2.28)
Foot (Metatarsal, Navicular)	8	1	9 (4.11)
Hand (metacarpal)	6	3	9 (4.11)
Knee	14	4	18 (8.22)
Ankle	9	2	11 (5.02) (a case of bilateral ankle involvement counted as two)
Elbow	6	1	7 (3.20)
Wrist	6	1	7 (3.20)
Bone marrow	–	1	1 (0.46)
Site not mentioned	3	1	4 (1.83)
Total	188	35	223 (219 patients)

another. 53.9% had isolated spinal involvement and another 8.7% had another associated lesion (Table 2). The knee joint (8.2%) was the second most commonly involved site, followed by the hip joint (5.5%). 31 patients (14.2%) had TB lesions at multiple sites including pulmonary and EPTB, which includes bones and joints and other organs (Table 3). Of these, 4 patients each had lesions at two distinct skeletal sites.

Table 3 – Skeletal involvement as part of multifocal/disseminated TB.

S. No. (patient with multifocal TB)	Sites of lesions					
	Spine	Chest (incl. lungs and pleura)	Lymph node	Abdomen	Other bones	Other sites
1		✓			Thumb	
2	✓					Miliary TB
3	✓	✓				
4	✓				Femur	
5		✓			Knee	
6		✓			Both ankles	
7		✓			Hip	
8	✓	✓				
9	✓	✓				
10		✓			Bone (site not mentioned)	
11			✓		Knee	
12					Hand + Foot	
13	✓			✓		
14	✓	✓				
15					Hand	Upper back
16	✓	✓				
17		✓			Knee	
18	✓		✓			
19			✓		Knee	
20	✓	✓	✓			
21	✓	✓				
22	✓					TB meningitis
23	✓				Elbow	Miliary TB
24	✓	✓	✓			
25	✓	✓				
26	✓	✓				
27	✓	✓				
28	✓			✓		
29	✓	✓				
30		✓			Wrist	
31					Bone marrow	Disseminated TB
Total	19	19	5	2	14	5

Table 4 – Site of spinal lesions.

S. No.	Site name	Total patients	Percentage
1	Cervical	6	4.38
2	Dorsal	48	35.04
3	Lumbar	43	31.39
4	Sacral	1	0.73
5	Cervico-Dorsal	1	0.73
6	Dorso-Lumbar	9	6.57
7	Lumbo-Sacral	11	8.03
8	Cervico-Dorso-Sacral	1	0.73
9	Dorso-Lumbo-Sacral	1	0.73
10	Site not specified	16	11.69
	Total	137	100

4.3. *Sites of spinal disease*

The dorsal and lumbar vertebrae were the most commonly affected segments of the spinal column accounting for 75.2% of all spine TB cases where site of spinal lesion was documented (Table 4). Another 17.4% had disease spanning two spinal segments while 2 patients (1.7%) had more extensive disease involving three different spinal segments.

4.4. *Type of cases*

Out of 219 cases, 172 cases (78.5%) were new cases who took ATT for skeletal TB. 163 patients (74.4%) received Category I regime prescribed under RNTCP and 6 (2.7%) were put on Category III regime; 3 patients (1.4%) received non-DOTS regime. 47 patients (21.5%) with previous history of ATT were put on Category II treatment.

5. Discussion

Skeletal TB refers to tuberculosis involving bones and/or joints. Evidence of skeletal TB has been identified in Egyptian mummies dating back to 9000 BCE.[7,8] A study of 483 pre-Columbian skeletons in Chile has shown lesions consistent with bony tuberculosis in 2% of cases.[9] In various studies, skeletal TB has been reported to account for 10–35% of EPTB cases and overall almost 2% of all TB cases.[10–14]

Our study was conducted at an RNTCP District TB Centre in the heart of Delhi. As of December 2012 (the end of our study period) RNTCP was capturing 70% of all TB cases in the country.[15] As our Clinic has been consistently meeting RNTCP case detection norms over the years, it can be reasonably assumed to have captured 70% of incident cases in its area of service and the data presented are a reliable representation of epidemiological features of TB in the community served.

The Karol Bagh area has one of the biggest markets in India, and because of this, our study group included a big migrant population who were in Delhi for employment. They were mainly from the low socio-economic class and came from different parts of India. In our study, 27.4% of all TB cases were due to EPTB. This is much higher than the current national figure of 14.9% but lower than the 35.4% rate of EPTB reported from Delhi in 2013.[3]

The proportion of skeletal TB was 7.1% of all EPTB cases and 1.94% of all TB patients in our study. The corresponding figures reported by TRC, Chennai are 11% of EPTB cases and 2% of all TB cases.[4] An RNTCP review of EPTB in 2000–01 reported a skeletal TB rate of 8.9% among all new EPTB cases.[1] The rate of skeletal TB has clearly not shown a major decline with the ongoing implementation of RNTCP. The rate even remains comparable to that in 483 pre-Columbian skeletons in Chile.[7] Fortunately, it has not demonstrated any upward trend, even with the HIV epidemic in India. However, skeletal TB accounted for 7.1% of all extra-pulmonary cases of tuberculosis, which is less in comparison with the other study reports.

As per our study, skeletal TB predominantly affects the young Indian population with incidence peaking in the second and third decades of life. This also shows that skeletal TB, like pulmonary TB, affects the productive population of India and its control is important for national development. The female gender (53%) is only marginally more affected than its male counterpart. In males, skeletal involvement reaches its peak in the second decade whilst in females the incidence peaks in the third decade.

In our study, 172 patients (78.5%) were new cases. No cases of DRTB with skeletal involvement were detected at the District Tuberculosis Centre till the end of our study period although diagnostic (culture and drug sensitivity testing) facilities for all Drug Resistant TB (DR TB) suspects based on standard RNTCP guidelines were in operation during the period 2009–2012 of the study. This is consistent with the hypothesis that skeletal TB is paucibacillary and responds well to antitubercular treatment.

Tuberculosis commonly involves joints more than long bones. There were only 8 cases (3.7%) involving long bones in our study. 18 cases (8.2%) had hand and feet involvement. Conversely, 55 patients (25.1%) had joint involvement. Skeletal TB remains one of the commonest differential diagnoses of monoarticular arthritis in India.

The spine was the most commonly involved skeletal site affecting 62.6% of all cases (137). 118 cases (53.9%) had isolated spinal column involvement while 8.7% had multifocal or disseminated TB. The next commonly involved sites were the knee (18 cases, 8.2%) and hip joints (12 cases, 5.5%).

In a similar study of 1074 cases of skeletal tuberculosis conducted at Banaras Hindu University Hospital (1965–67), spine was the most common site of skeletal involvement (440 cases, 41%), followed by knee joint (89 cases, 8.3%). There were 87 cases (8.1%) with disseminated skeletal TB.[16]

Spinal tuberculosis is not common in the western world. Most of the patients with spinal tuberculosis in developed countries are immigrants from countries where tuberculosis is endemic. In a study of 729 patients with tuberculosis over a 6-year period (1999–2004), conducted in the United Kingdom, approximately 8% (61 cases) had musculoskeletal involvement and nearly 50% of these patients had spinal involvement. Most of the patients (74%) were immigrants from the Indian subcontinent.[17]

The rate of spinal TB in our study is much higher than reported in any of the aforesaid studies. This could be because of better awareness and improved diagnostic modalities, or it could reflect a relative decline in TB affecting non-vertebral sites. It could also be because private medical practitioners in India are referring cases of spinal TB to RNTCP more often than before. Increased prevalence of spinal TB has its implications.

For the DOTS centre, it is important that the health care providers are sensitized about the complications of spinal TB. Patients with spinal TB have to be often provided anti-tubercular medicines at home, as they may be on strict bed rest. In case of worsening of neurological status while under treatment, patients need to be urgently referred to higher centres for further evaluation and management. From the working patient's perspective, bed rest and residual disabilities can have serious socio-economic repercussions.

6. Conclusion

Skeletal TB remains an important segment of EPTB cases diagnosed and treated under RNTCP, and its rate has not shown a major decline with implementation of RNTCP. The high numbers of patients with spinal TB reporting to RNTCP for treatment calls for close co-ordination between managing orthopaedic surgeons, treating physicians and DOT Providers to ensure adequate patient care. Sensitisation of the concerned personnel should further improve RNTCP service delivery.

Conflicts of interest

The authors have none to declare.

Acknowledgement

The authors wish to acknowledge the contributions of Dr Jagannathan Srinivasan and his team, Sarada Research Labs, Bangalore, for the e-TBPMS data; Sri Girjapati Tiwari and staff of the medical records section of Ramakrishna Mission Free TB Clinic in tracing patient documents and contacting patients; and also the RNTCP staff and Community DOT Providers of Ramakrishna Mission Free TB Clinic for help with data corroboration.

REFERENCES

1. Wares F, Balasubramanian R, Mohan A, Sharma SK. Extra pulmonary tuberculosis, management and control. In: Wares F, Balasubramanian R, Mohan A, Sharma SK, eds. In: *S.P. Agarwal and L.S. Chauhan's tuberculosis control in India*. Elsevier; 2005:95.
2. TB India 2012. *RNTCP status Report*. Nirman Bhawan, New Delhi 110011: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2012:116–117. TB India 2014, pp. 67–8.
3. TB India 2014. *RNTCP status Report*. Nirman Bhawan, New Delhi 110011: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2014:67–68.
4. Maurya AK, Kant S, Nag VL, Kushwaha RA, Dhole TN. Trends of anti-tuberculosis drug resistance pattern in new cases and previously treated cases of extrapulmonary tuberculosis cases in referral hospitals in northern India. *J Postgrad Med*. 2012;58(July–September (3)):185–189.
5. Isaakidis P, Das M, Kumar AM, et al. Alarming levels of drug-resistant tuberculosis in HIV-infected patients in Metropolitan Mumbai, India. *PLoS ONE*. 2014;9(10):e110461.
6. RNTCP. *Training Module for Medical Practitioners*. Nirman Bhawan, New Delhi 110011: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; July 2007:47.
7. Daniel TM, Bates JH, Downes KA. History of tuberculosis. In: Bloom BR, ed. In: *Tuberculosis: pathogenesis, protection, and control*. Washington: American Society for Microbiology; 1994:13.
8. Hershkovitz I, Donoghue HD, Minnikin DE, et al. Detection and molecular characterization of 9000-year-old *Mycobacterium tuberculosis* from a Neolithic settlement in the Eastern Mediterranean. *PLoS ONE*. 2008;3:e3426.
9. Arriaza BT, Salo W, Aufderheide AC, Holcomb TA. Pre-Columbian tuberculosis in northern Chile: molecular and skeletal evidence. *Am J Phys Anthropol*. 1995;98:37.
10. Watts HG, Lifeso RM. Tuberculosis of bones and joints. *J Bone Joint Surg Am*. 1996;78:288.
11. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res*. 2004;120:316–353.
12. Teo HE, Peh WC. Skeletal tuberculosis in children. *Pediatr Radiol*. 2004;34:853.
13. Fanning A. Tuberculosis: 6. Extrapulmonary disease. *CMAJ*. 1999;160:1597.
14. Peto HM, Pratt RH, Harrington TA, et al. Epidemiology of extrapulmonary tuberculosis in the United States, 1993–2006. *Clin Infect Dis*. 2009;49:1350.
15. TB India 2012. *RNTCP status Report*. Nirman Bhawan, New Delhi 110011: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare; 2012. pp. 1, 8, 53–4.
16. Tuli SM. *Tuberculosis of the skeletal system: bones, joints, spine and bursal sheaths*. 4th ed. Jaypee Brothers; 2010:6.
17. Talbot JC, Bismil Q, Saralaya D, Newton DA, Frizzel RM, Shaw DL. Musculoskeletal tuberculosis in Bradford – a 6-year review. *Ann R Coll Surg Engl*. 2007;89(4):405–409.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Add-on prednisolone in the management of cervical lymph node tuberculosis

Moti Lal Bunkar [a], *Shashi Prakash Agnihotri* [b], *Prahlad Ral Gupta* [c,*], *Savita Arya* [d]

[a] *Senior Resident, Department of Respiratory Medicine, Govt Medical College, Kota, India*
[b] *Professor, Department of Respiratory Medicine, SMS Medical College, Jaipur, India*
[c] *Professor and Head, Department of Respiratory Medicine, NIMS University, Shobha Nagar, Jaipur, India*
[d] *Resident, Department of Skin & VD, Govt Medical College, Kota, India*

ARTICLE INFO

Article history:
Received 1 January 2015
Accepted 15 May 2015
Available online 4 June 2016

Keywords:
Lymph node tuberculosis
Prednisolone
ATT

ABSTRACT

Studies defining role of systemic steroids in routine management of cervical lymph node tuberculosis (CLNTB) are too few and inconclusive. The present study was carried out to define the role of add-on prednisolone in the management of CLNTB. Patients of CLNTB were randomized into two groups. Group I patients received DOTS Category I treatment along with prednisolone 1 mg/kg for first 4 weeks and then tapered down. Group II patients received DOTS Category I treatment along with placebo. Patients were kept under close follow up for 6 months. Response to therapy and adverse drug reactions, if any, were recorded.

A total of 120 patients completed the study protocol. The two groups were similar with respect to age, sex, smoking, alcoholism, and clinical profile ($p > 0.5$). At 2 months, 54 out of 60 patients in Group I showed symptom relief when compared with 44 out of 60 patients in Group II ($p < 0.001$). Abscess, sinus, and/or appearance of new lymph node/s were noted in 3 and 13 patients in Group I and Group II, respectively ($p < 0.001$). Complete resolution was seen in 57 patients in Group I when compared with only 40 patients of Group II and sequel in form of residual LN was noted in three patients of Group I when compared with 20 in Group II ($p < 0.001$). Gastrointestinal side effects were reported by higher number of patients in Group I but skin rashes and joint pain were fewer when compared with Group II ($p > 0.05$). All the adverse reactions were transient and amenable to symptomatic treatment.

1. Introduction

The commonest form of extra pulmonary tuberculosis (EPTB) in humans is peripheral lymph node tuberculosis (PLNTB). The reported prevalence of the disease is 5% and 30–55% of all the TB and EPTB cases, respectively.[1,2] Like all other forms of TB, PLNTB is also managed with standard anti-tubercular (ATT) drugs/directly observed treatment strategy (DOTS) Category I under RNTCP,[3] but some of these patients often show up with

* *Corresponding author P.R. Gupta at*: A-66, Shubhash Nagar Shopping Centre, Jaipur 302016, India.
E-mail address: Guptapr_dr@hotmail.com.

http://dx.doi.org/10.1016/j.ijtb.2015.05.002

appearance of new nodes, increase in the size of existing nodes and/or sinus formation while on ATT and require surgical intervention.[4]

Add-on steroids to ATT have led to better outcomes in many forms of EPTB including pleural effusion,[5] pericardial effusion,[6] and tubercular meningitis. Anecdotal reports are also available; they show that add-on steroids are useful in the management of mediastinal lymphadenitis as well,[7] but studies defining the role of add-on steroids in routine management of PLNTB are too few and inconclusive.[8]

Since cervical lymph node tuberculosis (CLNTB) is the most common form of PLNTB,[9] and it is also the most cosmosensitive form of the disease, the present study was carried out to define the role of add-on prednisolone in its management.

2. Materials and methods

All the patients presenting with cervical lymphadenopathy between 1st April 2011 to 30th April 2013 at the Institute of Respiratory Diseases, Sawai Man Singh Medical College, Jaipur, Rajasthan, were recruited for the study. Permission of the ethical committee was obtained vide No. 453/MC/EC/17/12/2012. The trial was registered with clinical trial registry vide No. CTRI/2014/12005299. After giving full information regarding the nature of the study, a written consent was obtained from all the patients.

These patients were then re-evaluated with detailed clinical history, thorough physical examination and investigations including skiagram chest PA view, complete blood counts, complete urine examination, random blood sugar, HIV serology, sputum smear for acid fast bacillus, and Mantoux skin test. Ultrasound abdomen and contrast enhanced computerized tomography of thorax/abdomen/head were also done, as and when required.

A thorough examination of the enlarged lymph node/s (LN/s) was undertaken that included the site, size, number, tenderness, consistency, and mobility. Patients with diabetes mellitus, hypertension, acid peptic disease, and those with poor response to treatment in the past and/or pre-formed LN abscess were excluded from the study. Pregnant women, alcoholics, HIV seropositives, and those refusing consent for the study were also excluded.

Fine needle aspiration of the largest LN was aseptically done in the remaining patients. The material so obtained was subjected to cyto-pathological and bacteriological examination to find out evidence of TB. Whenever the material was shown as insufficient, an excisional biopsy was also done and processed as above. Only those, who were found positive for TB on cyto/histo-pathology and/or bacteriology, were eligible for final inclusion in the study.

The study patients were randomized into two groups. **Group I** patients were put on DOTS Category I treatment along with prednisolone 1 mg/kg body weight for first 4 weeks, subsequently tapered to 0.5 mg/kg body weight for another 4 weeks and then tapered down by 5 mg every week to zero dose. **Group II** patients were put on DOTS Category I treatment along with placebo.

Patients were kept under close follow-up during the course of treatment and response to therapy as well as adverse drug reactions, if any reported by the patients, were recorded. Adverse reactions were first managed symptomatically and if persisting, then by transient withdrawal of drugs. Complications in the form of abscess, sinus formation or appearance of new LN were also recorded. An abscess was managed by repeated aspirations as advocated by Jha et al.[9] A sinus was managed surgically and new LN/s, by prolongation of ATT.

The data so collected were analyzed for statistical significance using Student's *t* tests for continuous variables and χ^2 tests for non-continuous variables.

3. Results

After exclusions, 120 patients completed the study protocol, 60 in each group. The demographic profile of the patients is shown in Table 1. The two groups were similar with respect to

Table 1 – Pretreatment profile of the study patients.

Parameter	Group I	Group II	*p*-Value
Mean age in years	27.5 ± 12.9	26.3 ± 11.7	≥0.5
Sex			
Male	24	22	≥0.5
Female	36	38	
Smoker	2	2	≥0.5
	58	58	
Alcoholic	10	6	≥0.5
	50	54	
Symptoms[a]			
Swelling	44	46	≥0.5
Fever	25	28	
Loss of appetite	20	18	
Loss of weight	19	14	
Fatigue	28	15	
LN examination			
Number			
1	28	35	≥0.5
2	14	10	
±3	18	15	
Local tenderness			
Yes	24	18	≥0.5
No	36	42	
Mobility			
Yes	58	58	≥0.5
No	2	2	
Location			
U/L	53	57	≥0.5
B/L	7	3	
Mantoux test			
≤10 mm	2	2	≥0.5
≥10 mm	58	58	
Lesion in skiagram chest			
Yes	4	2	≥0.5
No	56	58	
Cyto/histopathology			
Positive	54	53	≥0.5
Negative	6	7	
AFB in LN smear			
Positive	8	12	≥0.5
Negative	52	48	

AFB, acid fast bacillus; LN, lymph node.
[a] Some patients had more than one symptoms.

Table 2 – Response to therapy and complications.

Parameter	Group I	Group II	p-Value
Relief in symptoms at 2M			
Yes	54	44	<0.001
No	6	16	
Complications during therapy[a]			
Abscess	2	8	<0.001
Sinus	0	5	
New LN	3	7	
Fate of LN at 6M			
Complete resolution	57	40	<0.001
Residual LN	3	20	

LN, lymph node.
[a] Some patients had more than one complications.

age, sex, smoking and alcoholic status, and clinical profile ($p > 0.5$).

Table 2 shows the response to therapy. At 2 months, more (54 out of 60) patients in Group I showed symptom relief when compared with Group II (44 out of 60, $p < 0.001$). Complications in form of abscess, sinus and/or appearance of new LN/s were noted in 3 patients in Group I when compared with 13 patients in Group II ($p < 0.001$). All these patients were managed by simple aspiration and prolonged therapy, but surgical exploration was required in three patients.

At the end of therapy, complete resolution was seen in 57 patients in Group I compared to only 40 patients of Group II and sequel in form of residual LN was noted in three patients of Group I when compared to 20 in Group II ($p < 0.001$). In Group I, the response was uniformly good, regardless of the number of LNs, i.e. complete resolution was seen in 27 out of the 28 patients (96.4%) with single LN and 30 out of the 32 patients (92.8) with ≥2 LNs. This was not so in Group II, where the complete response was seen in 28 out of 35 patients (80%) with single LN but only in 12 out of 25 patients (48%) with ≥2 LNs.

Table 3 shows the adverse reactions reported by the patients in the two groups. Gastrointestinal side effects were reported by higher number of patients in Group I. On the contrary, higher number of Group II patients reported skin rashes and joint pain. The differences, however, were statistically insignificant ($p > 0.05$) and were mostly transient and amenable to symptomatic treatment. None of the patients required permanent withdrawal of drugs and all the patients were able to complete 6 months chemotherapy.

Table 3 – Adverse reactions during therapy.

Adverse reactions	Group I	Group II	p-Value
Nausea/vomiting			
Yes	8	5	≥0.05
No	52	55	
Pain abdomen			
Yes	8	5	≥0.05
No	52	55	
Facial edema			
Yes	3	0	≥0.05
No	57	60	
Skin rashes			
Yes	1	7	≥0.05
No	59	53	
Joint pain			
Yes	2	15	≥0.05
No	58	45	

4. Discussion

The pretreatment profile of the patients in the two groups in the form of age, sex, symptoms, and status of lymphadenopathy was similar ($p > 0.5$), and thus the study data were valid for statistical analysis.

Only 40 out of the total 60 patients (66.67%) on ATT alone (Group II) showed complete resolution by 6 months. The response was still poor in patients with ≥2 LNs. Our results in CLNTB patients on ATT alone were inferior to those of Sharma et al.[10] and Kandala et al.[11] who could achieve success rates of 96% and 94% in their patients on DOTS CAT III treatment but were similar to those of Jain et al. (71.86%)[12] and Dixit et al. (63%).[13] Blaikely et al.[14] also reported complete resolution in only 82% of their patients on ATT alone. In comparison, as many as 57 patients (95%) of the group on add-on prednisolone to ATT (Group I) showed complete resolution by 6 months. Further, higher number of patients on the add-on prednisolone group (Group I) showed early symptomatic relief than those on ATT alone.

Campbell et al.[15] have noted flare ups in about 1/3rd of their lymphadenitis patients on ATT. In our study also, complications in form of abscess, sinus and/or new LN/s and sequel in the form of residual LN were reported in 13 patients (26.67%) on ATT alone but this was limited to only three patients (5%) on add-on steroid patients.

The above results of our study clearly shows that add-on oral prednisolone, given for first 3 to 4 months in tapering dosage improves clinical efficacy, decrease complications, and improves final outcomes in patients with CLNTB. This was, in all probabilities, due to the anti-inflammatory effect of steroids. Controlled studies on the usefulness of add-on steroids in the management of PLNTB are not available in the English literature.

Adverse reactions in the form of nausea/vomiting and pain abdomen were reported by higher number of patients on add-on steroids when compared with those on ATT alone ($p > 0.05$) but were similar to those observed by Blaikely et al.[14] in their patients on ATT alone and are known complications of ATT but add-on prednisolone might have also contributed to it in our patients. However, other complications such as skin rashes and joint pains were less common in the add-on prednisolone group. Further, all the adverse reactions could be managed by symptomatic drugs alone and withdrawal of steroids was not required in any of the patients. Thus, the use of add-on prednisolone for such a short period was essentially safe.

In conclusion, this study shows that, add-on prednisolone led to faster symptomatic relief, lesser complications, and higher resolution rates in patients with CLNTB on ATT and is also safe. The requirement of surgical excision was also reduced in the patients put on add-on prednisolone to ATT.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Asghar RJ, Pratt RH, Kammerer JS, Navin TR. Tuberculosis in south Asians living in the United States, 1993–2004. *Arch Intern Med*. 2008;168:936–942.
2. Shafer RW, Edlin BR. Tuberculosis in patients infected with human immunodeficiency virus: perspective on the last decade. *Clin Infect Dis*. 1996;22:683–704.
3. Arora VK, Gupta R. Trends of extrapulmonary tuberculosis under revised national tuberculosis control programme: a study from south Delhi. *Indian J Tuberc*. 2006;53:77–83.
4. Subrahmanyam M. Role of surgery and chemotherapy for peripheral lymph node tuberculosis. *Br J Surg*. 1993;80:1547–1548.
5. Mansour AA, Rbeay AI. Adjunct therapy with corticosteroids or paracentesis for treatment of tuberculous pleural effusion. *East Mediterr Health J*. 2006;12:504–508.
6. Reuter H, Burqess LJ, Louw VJ, Doubell AF. The management of tuberculous pericardial effusion: experience in 233 consecutive patient. *Cardiovasc J S Afr*. 2007;18:20–25.
7. Nemir RL, Cardona J, Vagiri F, Toledo R, et al. Prednisone as an adjunct in the chemotherapy of lymph node bronchial tuberculosis in childhood: a double blind study II – further term observations. *Am Rev Respir Dis*. 1967;95:402–410.
8. Kadhiravan T, Deepanjali S. Role of corticosteroids in the treatment of tuberculosis: an evidence based update. *Indian J Chest Dis Allied Sci*. 2010;52:153–158.
9. Jha BC, Dass A, Nagarkar NM, Gupta R, Singhal S. Cervical tuberculous lymphadenopathy: changing clinical pattern and concepts in management. *Postgrad Med J*. 2001;77:185–187.
10. Sharma S, Sarin R, Khalid UK, Singla N, Sharma PP, Behera D. Clinical profile and treatment outcome of tuberculous lymphadenitis in children using DOTS strategy. *Indian J Tuberc*. 2010;57:4–11.
11. Kandala V, Kalagani Y, Kondapalli NR, Kandala M. Directly observed treatment short course in immunocompetent patients of tuberculous cervical lymphadenopathy treated in revised national tuberculosis control programme. *Lung India*. 2012;29:109–113.
12. Jain NK, Bajpai A, Jain S. Outcomes of category III and I in immunocompetent patients of tuberculous lymphadenopathy treated in revised national tuberculosis control programme. *Lung India*. 2010;27:115–117.
13. Dixit R, Shelat GV, Gami S, Sharma S, Jindal S. Efficacy of Category III treatment regimen for tuberculous cervical lymphadenopathy.Indian Revised National Tuberculosis Control Programme (RNTCP). *Chest*. 2007;132:132 (meeting abstract).
14. Blaikley JF, Khalid S, Ormerod LP. Management of peripheral lymph node tuberculosis in routine practice: an unselected 10-year cohort. *Int J Tuberc Lung Dis*. 2011;15:375–378.
15. Campbell IA. The treatment of superficial tuberculous lymphadenitis. *Tubercle*. 1990;71:1.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Tuberculosis mortality in a rural population from South India

C. Kolappan *, *R. Subramani*, *S. Swaminathan*

National Institute for Research in Tuberculosis, Chennai, India

ARTICLE INFO

Article history:
Received 3 February 2015
Accepted 13 July 2015
Available online 4 June 2016

Keywords:
Mortality rate
Verbal autopsy
Cause of death
Tuberculosis mortality
TB

SUMMARY

Background: General mortality rate (GMR) is an essential indicator for assessing the health status of a community. Tuberculosis (TB) mortality is an indicator for the Millennium Development Goal for 2015.

Methods: This community-based retrospective survey was conducted in 2007–2008 on a sample of 114,605 rural populations living in 56 villages randomly selected from 218 villages in Tiruvallur district, South India, where the DOTS strategy was implemented in 1999. All the permanent residents of the households were registered and information on occurrence of death was recorded. All the deaths were investigated by verbal autopsy (VA) using standardized methods.

Results: A total of 719 deaths were registered. The GMR and tuberculosis mortality rate (TMR) were 648 (95% CI: 568–727) and 39 (95% CI: 25–52) per 100,000 p-yrs, respectively. The GMR increased with age, and was higher in males than females at all ages. The TMR was higher in males than females and the overall male:female ratio was 5:1.

Conclusion: TB was the 6th leading cause of death overall and the 2nd leading cause among men in this area. Strategies to reduce TB death should be implemented and the impact should be monitored by repeat VA studies.

1. Introduction

India has about nine million deaths a year, about one in six of all deaths worldwide and majority of these do not have a certified cause.[1] The Civil Registration System which records births and deaths in India is unreliable due to gross under-registration. The Medical Certification of Causes of Death is largely confined to selected urban settings only. A reliable assessment of disease-specific mortality rates is not yet possible in many parts of India, either because the underlying cause of the terminal illness was never known or because the relevant information was not recorded. Verbal autopsy (VA) is a research tool that has been used to determine probable causes of death in cases where there was no medical record or formal medical attention given. The Global Plan to Stop TB sets out the most effective approaches based on best estimates and projections of the Tuberculosis (TB) epidemic, as well as the

* *Corresponding author at:* Epidemiology unit, National Institute for Research in Tuberculosis, No. 1, Sathyamoorthy Road, Chetput, Chennai 600 031, India. Tel.: +91 44 28369500; fax: +91 44 28362528.
E-mail address: kola155@rediffmail.com (C. Kolappan).

http://dx.doi.org/10.1016/j.ijtb.2015.07.005

resources needed to support comprehensive TB control and priority research.[2] In 2006, the Stop TB partnership launched the Global Plan to Stop TB 2006–2015, a roadmap for scaling up prevention and treatment, for research and development, and for financing. The plan's goals included halving TB deaths compared to 1990 levels by 2015 – still a target today.[3] Reduction of TB mortality in the community is an indicator for effectiveness of TB control measures. This retrospective follow-up mortality survey in 2007–2008 collected data on TB mortality in the community from a rural area in South India where DOTS strategy was implemented in 1999.

1.1. *Objectives*

To estimate the general mortality rate (GMR) and TB mortality rate (TMR) for the target population in the Tiruvallur district of Tamilnadu.

2. Methodology

2.1. *Sampling*

Assuming an annual incidence rate of death of 9 (95% CI: 8–10) per 1000 population, the sample size required was calculated to be 34,263 for this mortality survey.[4] This sample size would have yielded about 308 deaths, which may not be sufficient to detect enough TB deaths, which need to be further stratified by age and sex. Further, an increase in sample size would improve the precision of death rate estimates. Therefore, the sample size was increased about threefold to 114,605 persons residing in a sample of 56 villages randomly selected from the 218 villages in Tiruvallur district, South India, where DOTS strategy was implemented in 1999. A stratified cluster sampling design was employed. A simple random sample of village and urban units were selected proportionate to the census population.

2.2. *Registration*

Trained field investigators carried out the house-to-house enumeration during the period from 29/01/2007 to 29/04/2008. All the permanent residents in a household were registered in the survey. During registration, the household number, names of the members in the household, age in completed years, and gender of the individuals were recorded. In addition, information on occurrence of death in each household, on or after 'Pongal festival' day 2007 (15th January 2007) was recorded. 'Pongal' is a major New Year festival in this region. All household forms reporting deaths were handed over to the supervisors for detailed VA to ascertain the underlying cause of death. The Institutional Ethics Committee of National Institute for Research in Tuberculosis, Chennai had approved this study. The consent from the participants was obtained orally after briefing about the study.

2.3. *Follow-up*

Each person was followed up from 'Pongal' day to the date of registration/death/migration (a permanent resident who was moved to another region). The follow-up period was measured in person years (p-yrs). Each household was visited only once (at the time of registration only).

2.4. *VA*

VA is an investigation of chain of events, circumstances, symptoms and signs of illness leading to death, through an interview of the Head of the family or any other adult household member of the deceased. Supervisors were trained on VA methodology, which was developed in Tamilnadu and is being used in Sample Registration System (SRS) in India.[5] Specially trained supervisors conducted the VA. The instrument used was the standard form with addition of TB specific questions to collect past history of TB among the adult deaths irrespective of primary cause of death. The VA form consists of three separate sections. Section I deals with general information of the deceased and the respondent, section II is a semi-structured questionnaire to probe the nature of symptoms and signs the deceased had immediately preceding the death, and section III deals with the written narrative. The narrative was written in the local language as narrated by the respondent and included information on the symptoms in the order of occurrence, the nature of medical help sought, findings of investigation reports, and hospital diagnosis and records whenever available. The supervisors were non-medical graduates with knowledge of local language and trained in VA instrument. The respondents were the family members or close associates of the deceased. The average recall period was 354 days.

2.5. *Salient features of VA instrument*

VA is an epidemiological tool of proven value for determining cause-specific mortality. Open-ended narrative part is the most important factor in the classification of cause of death. This VA instrument had been well validated and could ascertain leading causes of death among the population. A standardized Symptom list was used as a filter to define additional probing questions related to a particular symptom and also to ascertain sufficient information on the symptoms of the illness prior to death if the respondent had difficulty in remembering any major symptom.[5–7]

2.6. *Quality control*

Five percent of household forms and VA forms were randomly selected and crosschecked by coordinators/supervisors and corrected information was considered whenever any discrepancies were found.

2.7. *Cause of death*

WHO recommends that all primary tabulations on causes of death should be based on the underlying cause of death. The underlying cause of death is defined as: ''The disease which initiated the chain of events leading directly to death or the circumstances of the accident or violence which produced the fatal injury.''

Table 1 – Age, sex distribution, and enumeration status of the study population.

Age groups in years	Males			Females			Males + Females		
	Alive *n* (%)	Dead *n* (%)	Migrated *n* (%)	Alive *n* (%)	Dead *n* (%)	Migrated *n* (%)	Alive *n* (%)	Dead *n* (%)	Migrated *n* (%)
<15	13,811 (98.4)	9 (0.1)	212 (1.5)	12,996 (98.4)	10 (0.1)	205 (1.6)	26,807 (98.4)	19 (0.1)	417 (1.5)
15–44	28,952 (98.1)	65 (0.2)	499 (1.7)	28,278 (96.3)	44 (0.1)	1037 (3.5)	57,230 (97.2)	109 (0.2)	1536 (2.6)
45–64	10,180 (97.8)	151 (1.5)	82 (0.8)	11,204 (98.5)	86 (0.8)	87 (0.8)	21,384 (98.1)	237 (1.1)	169 (0.8)
65+	2869 (93.3)	186 (6.0)	21 (0.7)	3415 (94.3)	168 (4.6)	38 (1.0)	6284 (93.8)	354 (5.3)	59 (0.9)
All	55,812 (97.9)	411 (0.7)	814 (1.4)	55,893 (97.1)	308 (0.5)	1367 (2.4)	111,705 (97.5)	719 (0.6)	2181 (1.9)

2.8. *Coding of cause of death*

Two medical officers specially trained in reviewing VA reports and coding cause of all deaths as per ICD-10 (including HIV-associated deaths classified as certain infectious and parasitic disease) assigned underlying cause of death and coded all completed VA forms independently. VA reports with disagreement between two medical officers in the underlying cause of death were adjudicated by an adjudicator experienced in coding cause of death from VA forms. The adjudicator's code was considered final for classification of deaths.

2.9. *Data processing and analysis*

The coded forms were computerized by double entry system and the mistakes were corrected wherever necessary using Epi Info V 6.04d, CDC, and USA.[8] The data were analyzed to estimate the GMR and TMR per 100,000 p-yrs. The cluster design was accounted for in the 95% confidence interval calculation and *p*-value <0.05 was considered as statistically significant.

3. Results

In this study, 97.5% of persons were present from 25,767 sample households at the time of investigation. The sample population comprised 49.8% (57,037/114,605) of males (Table 1). Out of the total deaths registered, 57.2% deaths occurred among males. The migration rate was 1.9% and was highest among females aged 15–44 years. Migration had occurred in the registered population between the date of registration and date of interview. The crude death rate was 6 per 1000 persons. GMR for males was 742 (95% CI: 634–851) per 100,000 p-yrs and for females, it was 554 (95% CI: 472–635) per 100,000 p-yrs (Table 2). The difference was statistically significant ($p = 0.0001$). The GMR in this study population was 648 (95% CI: 568–727) per 100,000 p-yrs. The GMR increased with age in both males and females. For all age groups except the youngest age group, females had lower GMR than males. There were 43 (6%) TB deaths out of 719 total deaths and the TMR was 39 (95% CI: 25–52) per 100,000 p-yrs. The TMR was significantly higher among males than females (65 vs. 13 per 100,000 p-yrs) and was statistically significant ($p < 0.0001$) (Table 3).

The major causes of mortality include non-communicable diseases like myocardial infarction, stroke, neoplasm, Diabetes mellitus, COPD, and chronic renal failure (Table 4). TB and diarrheal diseases were the only communicable diseases in the top ten causes of death. TB ranks the 6th cause of death in all persons and number 2 in males along with Senility (Table 4), number 7 amongst 15- to 44-year olds and number 3 amongst 45- to 64-year olds (Table 5). Nearly one-fourth of the deaths could not be assigned a specific cause but were classified under Senility, Ill-defined/unclassified symptoms, Pyrexia of unknown origin, and Sudden death. Myocardial infarction, Road traffic accidents, and Suicide were the top three causes in the younger age group of 15–44 years. In the middle age group (45–64 years), Myocardial infarction, Neoplasm, and TB were the three major causes of death (Table 5), while in the older age group (≥65 years), Senility, Myocardial infarction, and Stroke were the top three causes.

Table 2 – General mortality rate (GMR) per 100,000 p-yrs by age and gender.

Age groups in years	Males			Females			Difference in rates (Males and Females) *p* value	Males + Females		
	Death *n*	p-yrs *n*	Rate *n* (95% CI)	Death *n*	p-yrs *n*	Rate *n* (95% CI)		Death *n*	p-yrs *n*	Rate *n* (95% CI)
<15	9	13,610	66 (24–108)	10	12,803	78 (26–130)	0.7167	19	26,413	72 (43–101)
15–44	65	28,732	226 (164–289)	44	28,304	155 (101–210)	0.053	109	57,036	191 (145–238)
45–64	151	10,133	1490 (1244–1736)	86	11,102	775 (605–945)	<0.0001	237	21,234	1116 (956–1276)
65+	186	2898	6419 (5321–7517)	168	3429	4900 (4129–5670)	0.0088	354	6327	5595 (4957–6234)
All	411	55,373	742 (634–851)	308	55,637	554 (472–635)	0.0001	719	111,010	648 (568–727)

p-yrs: Person-years.

Table 3 – Tuberculosis mortality rates (per 100,000 p-yrs) by age and gender.

Age groups in years	Males			Females			Difference in rates (Males and Females)	Males + Females		
	Death	p-yrs	Rate	Death	p-yrs	Rate	*p*-value	Death	p-yrs	Rate
	n	*n*	*n* (95% CI)	*n*	*n*	*n* (95% CI)		*n*	*n*	*n* (95% CI)
<15	0	13,610	0	0	12,803	0	–	0	26,413	0
15–44	2	28,732	7	1	28,304	4	0.5725	3	57,036	5 (0–11)
45–64	18	10,133	178 (95–260)	5	11,102	45 (4–86)	0.0033	23	21,234	108 (64–153)
65+	16	2898	552 (217–887)	1	3429	29	0.0001	17	6327	269 (117–420)
All	36	55,373	65 (38–92)	7	55,637	13 (3–22)	<0.0001	43	111,010	39 (25–62)

p-yrs: Person-years.
Note: Confidence intervals could not be calculated since death events were fewer than 5.

Table 4 – Top ten causes of Death – by gender.

Cause of death (ICD10 codes)	Rate/100,000 p-yrs (Rank)		
	All persons	Males	Females
Myocardial infarction (I21, I22)	104 (1)	144 (1)	63 (2)
Senility (R 54)	84 (2)	65 (2)	102 (1)
Neoplasm (CO2-D37)	59 (3)	54 (4)	61 (3)
Stroke (I 64)	53 (4)	58 (3)	49 (4)
Ill-defined/unclassified symptoms (R 99)	50 (5)	38 (6)	61 (3)
Tuberculosis (A15-A19)	39 (6)	65 (2)	13 (9)
Road traffic accidents (V02-V99)	29 (7)	49 (5)	–
Pyrexia of unknown origin (R 50)	23 (8)	20 (10)	27 (5)
Diabetes Mellitus (E 14)	21 (9)	25 (7)	16 (7)
Diarrheal diseases (A 09)	18 (10)	25 (7)	11 (10)
Chronic Obstructive Pulmonary diseases – COPD (J 44)	18 (10)	23 (8)	13 (9)
Sudden death (R 96)	–	22 (9)	13 (9)
Chronic renal failure (N18, N19)	–	–	18 (6)
Suicide (X68-X76)	–	20 (10)	14 (8)
Fall (W01-W18)	–	–	18 (6)

'–' no death.
p-yrs: person-years.

Table 5 – Top ten causes of death – by age.

Cause of death (ICD10 codes)	Rate/100,000 p-yrs (Rank)			
	Age groups in years			
	<15	15–44	45–64	65+
Myocardial infarction (I21, I22)	–	46 (1)	235 (1)	616 (2)
Senility (R 54)	–	–	–	1470 (1)
Neoplasm (CO2-D37)	8 (1)	18 (4)	165 (2)	300 (6)
Stroke (I 64)	–	–	104 (4)	569 (3)
Ill-defined/unclassified symptoms (R 99)	4 (2)	12 (5)	71 (5)	506 (4)
Tuberculosis (A15-A19)	–	5 (7)	108 (3)	269 (7)
Road traffic accidents (V02-V99)	–	30 (2)	38 (8)	–
Pyrexia of unknown origin (R 50)	4 (2)	–	–	332 (5)
Diabetes Mellitus (E 14)	–	–	57 (6)	174 (10)
Diarrheal diseases (A 09)	–	9 (6)	24 (10)	–
Chronic Obstructive Pulmonary diseases – COPD (J 44)	–	–	33 (9)	205 (9)
Sudden death (R 96)	–	–	47 (7)	–
Chronic renal failure (N18, N19)	–	–	47 (7)	–
Suicide (X68-X76)	–	25 (3)	–	–
Fall (W01-W18)	4 (2)	–	–	221 (8)
Jaundice (R17)	–	–	24 (10)	–

'–' no death.
p-yrs: person-years.

4. Discussion

The study was conducted in 2007–2008 to collect data on the GMR and cause specific mortality rates among the general population in this rural area near Chennai city, South India. These data are needed to measure progress against global TB control targets. Also, the estimates of mortality after eight years of DOTS implementation in the intensively monitored ''study area'' could provide useful information on program efficiency. The conventional method involves prospective follow-up of study population for a period of one year to report on the deaths occurring during the follow-up period. A health worker (HW) is deployed for each village/urban unit. The HW records all deaths occurring in the village during his routine weekly or biweekly visits and carryout VA preferably within 7–10 days after the event has occurred. We used a retrospective follow-up methodology in which the enumeration of the population and data on deaths occurring between the reference date and the date of enumeration was collected at the time of enumeration itself. An event of death is associated with strong emotional effect on the surviving members of the household, and it has been generally accepted that the recall of the event will be accurate up to one year. In this study, the average duration of recall period was 354 days. It can be safely assumed that the estimates of GMR are comparable to estimates obtained in prospective study design. Thus, the retrospective follow-up method is rapid and economical without compromising the accuracy of estimates of GMR.

The VA technique was initially developed for childhood and maternal mortality studies, but currently many studies on adult mortality also use the VA tool. The validity of VA is influenced by the cause of death per se and other factors related to the interviewer, respondent, recall period, and derivation of diagnoses from narrative forms.[5] Chandramohan et al. concluded that VAs by a panel of physicians performed better than an opinion-based algorithm, and the validity of VA diagnosis was highest for acute febrile illness and TB/AIDS.[6] Khan et al. reported that deaths coded as pulmonary TB (among adults aged ≥15 years) by VA had 92% sensitivity and 99% specificity when validated against hospital diagnosis.[7] However, Yang et al. reported that TB deaths diagnosed by VA had 62.2% sensitivity and 99.3% specificity.[9] Despite the possibility of misclassification, the cause specific mortality rates reported in our study should serve as baseline estimates. The crude death rate of 6 per 1000 persons reported in our study is lower than 8.2 per 1000 persons reported for rural population of Tamilnadu by the SRS in its provisional estimates for the year 2005.[10] Joshi et al. reported a crude death rate of 7.5 per 1000 for East and West Godavari districts of Andhra Pradesh (a neighboring state) for the period 2003–04.[11] In our study, males had higher GMR than females probably due to higher prevalence of health risk behaviors like smoking and alcoholism as evident from the reports published earlier.[12] The TB mortality rate in this study area was 39 per 100,000 p-years. As per WHO estimates in 2006, the tuberculosis mortality rate (TMR) in India was 28 per 100,000 persons.[13]

According to the WHO Global TB report, the estimated TMR in India for the year 2013 was 22 (95% CI: 14–32) per 100,000.[14] The reduction in TMR reported might be due to improved TB treatment under DOTS program. TMR is five times higher among males than among females. This gross difference may be explained by the higher prevalence of disease among males (M:F ratio of 5:1).[15] Also, it was reported that men were less likely to seek health care in the community.[16] In this study, the deaths due to TB was 6% of total deaths. Joshi et al. reported that 4% of total deaths were TB deaths in east and west Godavari districts.[11] Mahapatra reported 6.3% TB deaths in A.P. in 1991.[17] Gajalakshmi et al. reported 6% TB deaths in urban and 8% in rural Tamilnadu among persons aged 25–69 years during 1995–1998.[18] Murray et al. have estimated 8% TB deaths for India in 1990.[19] Kanungo et al. reported the overall mortality as 6.2 per 1000 p-yrs and TB mortality rate as 35 per 100,000 p-yrs from Kolkata study conducted in 2003.[20] These findings were all comparable with the TB mortality rates obtained in our study. We observed that there were 43 (6%) TB deaths out of 719 total deaths. The TMR was significantly higher among males than females (65 vs. 13 per 100,000 p-yrs) and was statistically significant ($p < 0.0001$). In the same area, we have earlier reported that male TB patients aged >45 years, with incomplete treatment, smokers, and alcoholics were at high risk of death during treatment.[21] The present study showed that 50% of deaths occurred in 6% of the total population aged ≥65 years which is not unexpected. It would be preferable to plan intervention strategies for each age and gender subgroup by looking at the cause specific mortality data. Deaths attributed to non-communicable diseases such as myocardial infarction (16%), stroke (8%), and neoplasms (9%) were determined. A specific cause of death that could not be assigned was 23%.

TB is still the major cause of communicable disease deaths in this community. Socio-economic conditions play an important role in the changing pattern of mortality and morbidity in an area. Periodic surveys to determine causes of death could help policy makers and planners to focus on the appropriate health programs and interventions needed. Such an exercise would also help determine if MDG and post-MDG goals are being attained, especially as related to TB.

4.1. *Limitations*

The mortality data were collected retrospectively in contrast to other mortality surveys in which the data were collected prospectively. The VA technique is still evolving and needs to be perfected because the validity varies widely between different causes of death. Important health indicators like Infant mortality rate could not be estimated, as infant deaths among total number of live births could not be collected in this retrospective data collection method. The findings from our study may not be representative of TMR of the rural population of India, as it is likely to vary depending on the efficiency of control measures implemented in different areas.

5. Conclusion

Mortality surveys can be carried out using a retrospective follow-up design, which is rapid and more cost effective than the conventional prospective design. Males have significantly higher GMR than females. The male TMR is five times higher

than the female TMR. The GMR and TMR may be less informative than cause-specific mortality data by age and gender subgroups, which can be used to plan intervention strategies.

Funding

Financial assistance was provided by the United States Agency for International Development (USAID) under the Model DOTS Project. The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflicts of interest

The authors have none to declare.

Acknowledgements

The authors acknowledge the contribution in training the supervisors on VA methodology and coding the underlying cause of death for the VA forms by Dr. V. Gajalaksmi MBBS, DPM, MSc (Epi) (Toronto, Canada), ScD (Epi) (Tampere, Finland) and her team and for adjudicating by Dr. V. Gajalaksmi from the Epidemiological Research Center, Chennai, India. We also acknowledge the contributions from the staff of epidemiology unit and cooperation of the community.

REFERENCES

1. Jha P, Gajalakshmi V, Gupta PC, et al. Prospective study of one million deaths in India: rationale, design, and validation results. *PLoS Med*. 2006;3:e18. http://dx.doi.org/10.1371/journal.pmed.0030018.
2. Stop TB Partnership. *The Global Plan to Stop TB, 2006-2015: actions for life: towards a world free of tuberculosis*. Geneva: WHO; 2006 (WHO/HTM/STB/2006.35) Available from: http://whqlibdoc.who.int/publications/2006/9241593997_eng.pdf.
3. Stop TB Partnership. *The global plan to stop TB 2011-2015: transforming the fight towards elimination of tuberculosis – reprinted with changes*. WHO; 2011 (WHO/HTM/STB/2010.2). Available from: http://whqlibdoc.who.int/publications/2010/9789241500340_eng.pdf.
4. Available from: http://home.clara.net/sisa.
5. Available from: http://cghr.org/wordpress/wp-content/uploads/2011/07/MDS-Study-Protocol.pdf.
6. Chandramohan D, Maude GH, Rodrigues LC, Hayes RJ. Verbal autopsies for adult deaths: their development and validation in a multi centre study. *Trop Med Int Health*. 1998;3:436–446.
7. Kahn K, Tollman SM, Garenne M, Gear JS. Validation and application of verbal autopsies in a rural area of South Africa. *Trop Med Int Health*. 2000;5:824–831.
8. Available from: http://www.cdc.gov/epiinfo.
9. Yang G, Rao C, Ma J, et al. Validation of VA procedures for adult deaths in China. *Int J Epidemiol*. 2006;35:741–748.
10. Available from: http://www.censusindia.gov.in/vital_statistics/SRS_Bulletins/SRS_Bulletins_links/SRS.
11. Joshi R, Cardona M, Iyengar S, et al. Chronic diseases now a leading cause of death in rural India—mortality data from the Andhra Pradesh Rural Health Initiative. *Int J Epidemiol*. 2006;35:1522–1529.
12. Kolappan C, Gopi PG, Subramani R, Narayanan PR. Selected biological and behavioural risk factors associated with pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2007;11:999–1003.
13. WHO Report. *Global Tuberculosis Control – Surveillance, Planning Financing*. Geneva: World Health Organization; 2006.
14. World Health Organization. *Global Tuberculosis Control: WHO report 2013*. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.11).
15. Kolappan C, Subramani R, Radhakrishna S, et al. Trends in the prevalence of pulmonary tuberculosis over a period of seven and half years in a rural community in south India with DOTS. *Indian J Tuberc*. 2013;60:168–176.
16. Santha T, Renu G, Friedon TR, et al. Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India. *Int J Tuberc Lung Dis*. 2003;7:258–265.
17. Mahapatra P. *Estimating National Burden of Disease: The Burden of Disease in Andhra Pradesh in 1990s*. Hyderabad: The Institute of Health Systems BK03/2001; 2001:246.
18. Gajalakshmi V, Peto R. Verbal autopsy of 80,000 adult deaths in Tamilnadu, South India. *BMC Public Health*. 2004;4:47.
19. Murray CJL, Lopez AD. *The Global Burden of Disease*. Geneva: World Health Organization, Harvard School of Public Health, World Bank; 1996.
20. Kanungo S, Tsuzuki A, Deen JL, et al. Use of verbal autopsy to determine mortality patterns in an urban slum in Kolkata, India. *Bull World Health Organ*. 2010;88:667–674. http://dx.doi.org/10.2471/BLT.09.073742.
21. Kolappan C, Subramani R, Kumaraswamy V, Santha T, Narayanan PR. Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. *Int J Tuberc Lung Dis*. 2008;12:81–86.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Original Article

Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis

Rajendra Prasad [a,*], *Abhijeet Singh* [a], *Rahul Srivastava* [a], *Giridhar B. Hosmane* [a], *Ram Awadh Singh Kushwaha* [a], *Amita Jain* [b]

[a] *Department of Pulmonary Medicine, King George Medical University, Lucknow, India*
[b] *Department of Microbiology, King George Medical University, Lucknow, India*

ARTICLE INFO

Article history:
Received 21 February 2015
Accepted 19 January 2016
Available online 16 June 2016

Keywords:
Adverse events
DOTS PLUS
Second-line drugs

ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is considered to be a worldwide problem with notoriously difficult and challenging treatment. Adverse events associated with second-line drugs (SLDs) can have severe impact on efficient management.
Objective: To know the frequency of adverse events due to SLDs in patients of MDR-TB.
Design: A prospective cohort analysis of 98 MDR-TB patients enrolled between June 2009 to February 2010 was conducted in Department of Pulmonary Medicine, King George Medical University, Lucknow, India. All the patients were provided standardized regimen. Adverse events associated with treatment were recognized primarily by clinical evidence and/or laboratory investigations that were advised at baseline and whenever clinically indicated during course of treatment. Adverse events were considered major if required permanent discontinuation or substitution of drugs.
Results: 119 adverse events were reported in 46 (46.9%) patients. The grouped adverse events were most commonly gastrointestinal that was observed with a frequency of 48 (40.3%) followed by ototoxicity in 28 (23.6%), and neurological in 21 (17.6%). 17 (17.4%) patients had major adverse events requiring permanent discontinuation or substitution of drugs that included deafness and tinnitus in 5 (5.1%) followed by psychosis in 4 (4.1%). None of the patients stopped complete regimen due to adverse events. The treatment success rate was observed to be 71 (72.4%).
Conclusions: MDR-TB can be cured successfully with appropriate combination of drugs if adverse events associated with them can be managed aggressively and timely. Newer and less toxic drugs are urgently needed to treat MDR-TB patients.

1. Introduction

Multidrug-resistant TB (MDR-TB) is defined as *Mycobacterium tuberculosis* resistant to Isoniazid and Rifampicin with or without resistance to other first-line drugs. The emergence of resistance to drugs used to treat tuberculosis, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective tuberculosis control. Out of the estimated global annual incidence of 9

* *Corresponding author*. Tel.: +91 8826406406.
E-mail address: rprasadkgmc@gmail.com (R. Prasad).
http://dx.doi.org/10.1016/j.ijtb.2016.01.031

million tuberculosis cases in 2011, 2.3 million were estimated to have been reported in India. The prevalence of MDR-TB among notified new and retreatment pulmonary tuberculosis patients are estimated to be 2.1% and 15%, respectively.[1] Patients may present with a variety of adverse events when second-line drugs (SLDs) are prescribed for MDR-TB management. Most of the adverse events are minor and can be managed without discontinuation of treatment. Some adverse events can be life threatening if not recognized and treated promptly. There are major concerns regarding SLDs in that they are expensive, have low efficacy, and more toxic as compared to first-line antituberculosis drugs.[2–4] There may be a severe impact on adherence and higher risk of default and treatment failure affecting outcome overall if such adverse events are not properly managed.[5] Several studies have highlighted regarding high potential of these SLDs to cause adverse events that have led to interruption of treatment in 20–60% of MDR-TB patients.[6–23] Very few have specifically reported frequency of adverse events in India.[24–27] The present study has been designed to know the frequency of adverse events encountered in patients receiving SLDs for treatment of MDR-TB at Lucknow, India.

2. Methods

It was a prospective cohort study performed among 132 consecutive patients of pulmonary tuberculosis referred from various districts of Uttar Pradesh, India between June 2009 and February 2010 in Department of Pulmonary Medicine and Department of Microbiology, King George Medical University, Lucknow, India, which is a WHO-recommended Intermediate Reference Laboratory (IRL) certified by Revised National Tuberculosis Control Programme (RNTCP) of India. The patients included in the study were either new or retreatment cases of pulmonary tuberculosis with proven culture positive for *M. tuberculosis* and resistant to at least Isoniazid and Rifampicin and having age more than 18 years. The retreatment cases received previously multiple courses of antitubercular drugs including five drugs – Streptomycin, Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide (SRHEZ), either daily (unsupervised) or DOTS Category II (supervised). The patients were excluded from the study if they (1) had not confirmed to be MDR-TB according to Drug Susceptibility Testing (DST) results, (2) had taken SLDs more than 1 month before confirmation of diagnosis, (3) had pregnancy, (3) were under 18 years of age, and (4) had concurrent major medical illnesses (chronic kidney disease, decompensated congestive heart failure, fulminant hepatic failure, acute gastritis, and seizure disorder) or major psychiatric illnesses (schizophrenia, depression) at baseline. These exclusions were as per the RNTCP current guidelines at the time of study.[28] All patients provided informed consent before participating in the study. Pretreatment investigations included sputum smear for AFB, culture for *M. tuberculosis* by conventional Löwenstein–Jensen media, DST by proportion method, complete hemogram (hemoglobin, total and differential leukocyte count, platelet count, and peripheral blood smear), chest X-ray, renal and liver function tests, and thyroid profile. All patients were routinely tested for human immunodeficiency virus (HIV) infection before initiation of treatment. All the patients were offered treatment given as per DOTS PLUS Protocol of RNTCP based on World Health Organization (WHO) Guidelines prevailing at that time.[28,29] The standardized regimen consisted of 6–9 months with six drugs – Kanamycin, Ofloxacin, Ethionamide, Cycloserine, Pyrazinamide, and Ethambutol, followed by 18 months Ofloxacin, Ethionamide, Cycloserine, and Ethambutol. The daily dosages prescribed were according to weight band: Kanamycin (500 mg); Ethionamide and Cycloserine (500 mg each); Ofloxacin (600 mg); Pyrazinamide (1250 mg), and Ethambutol (800 mg) for patients having weight less than 45 kg; for patients weighing ≥45 kg, the daily dose of Kanamycin was 750 mg, Ethionamide and Cycloserine was 750 mg, Ofloxacin 800 mg, Pyrazinamide 1500 mg, and Ethambutol 1250 mg. All of the drugs were provided free of cost. Treatment outcome was also defined according to the DOTS PLUS guidelines framed by RNTCP of India, as well as WHO,[28,29] as mentioned in Table 1. Patients were seen by doctors and staffs trained in RNTCP DOTS PLUS guidelines for clinical evaluation at monthly intervals during the intensive phase, and at three monthly intervals during the continuation phase until the end of treatment. Clinical, microbiologic, and radiologic response to treatment, weight, and possible adverse events were assessed at each follow-up visit and recorded in treatment cards. The main outcome variable was the occurrence of adverse events. All patients and their family members were counseled prior to treatment initiation, as well as during all follow-up visits, regarding possible adverse events and encouragement to report such events. Adverse events, if any, were recorded at each visit based on clinical evidence and subsequently managed as per protocol described in Table 2.[28,29] In addition to clinical evidence, certain

Table 1 – Definitions of various clinical outcomes.

Outcomes	Definitions
Cure	Patient of MDR-TB who has completed treatment and has been consistently culture negative with at least 5 consecutive negative results in the last 12–15 months or if one follow-up culture reported positive culture during the same period, and then provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, with clinical evidence of improvement.
Death	Patient of MDR-TB who dies for any reason during the course of treatment.
Failure	Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12–15 months are positive, or if any of the final three cultures are positive.
Default	A MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reason.
Smear conversion time	Time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive smears respectively, taken at least 1 month apart.
Culture conversion time	Time to smear and culture conversion was defined as the time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive cultures respectively, taken at least 1 month apart.

Table 2 – Definition of adverse events.

Adverse events	Definitions	Suggested management strategies
Nausea, vomiting, diarrhea, constipation, anorexia, and abdominal pain	Any documentation of nausea, vomiting, diarrhea, constipation, anorexia, and/or abdominal pain by healthcare worker/physician.	- Assess for dehydration; initiate rehydration if indicated. - Initiate antiemetic therapy. - Lower dose of suspected agent if this can be done without compromising regimen. - Discontinue suspected agent if this can be done without compromising regimen, rarely necessary. - Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. - Electrolytes should be monitored if vomiting is severe. - Reversible upon discontinuation of suspected agent. - Antidiarrheal agents, laxatives, and antispasmodic, as per requirement.
Gastritis	Any documentation of gastritis by healthcare worker/physician.	- H2-blockers, proton-pump inhibitors, or antacids. - Stop suspected agent(s) for short periods of time (1–7 days). - Lower dose of suspected agent, if this can be done without compromising regimen. - Discontinue suspected agent if this can be done without compromising regimen. - Severe gastritis, as manifested by hematemesis, melena, or hematochezia, is rare. - Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 h before or 3 h after antituberculosis medications). - Reversible upon discontinuation of suspected agent(s).
Hepatitis	Elevation of either serum transaminase or serum bilirubin at least 3 times the upper limit of normal values with symptoms or 5 times the upper limit of normal values without symptoms {normal ranges: AST (15–45 IU/L), ALT (15–45 IU/L), bilirubin (0–1.0 mg/dl)}.	- Stop all therapy pending resolution of hepatitis. - Eliminate other potential causes of hepatitis. - Consider suspending most likely agent permanently. - Reintroduce remaining drugs, one at a time, while monitoring liver function. - History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens. - Generally reversible upon discontinuation of suspected agent.
Depression	As diagnosed by TB physician and/or as judged by a psychiatrist.	- Offer group or individual counseling. - Initiate antidepressant therapy. - Lower dose of suspected agent if this can be done without compromising regimen. - Discontinue suspected agent if this can be done without compromising regimen. - Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. - Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. - History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment.
Psychosis	As diagnosed by TB physician and/or as judged by a psychiatrist.	- Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. - Initiate antipsychotic therapy. - Lower dose of suspected agent if this can be done without compromising regimen. - Discontinue suspected agent if this can be done without compromising regimen. - Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. - Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment. - Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.
Headache, dizziness, tinnitus, and vertigo	As per patient perception and complaining.	- Referral to otorhinolaryngologist. - Antivertigo drugs and/or change to less ototoxic drug preferred over lowering of dose.

Table 2 (*Continued*)

Adverse events	Definitions	Suggested management strategies
Hearing loss/deafness	As per patient's complaint and hearing loss confirmed by physical examination and/or audiometry in consultation with otorhinolaryngologist.	- Document hearing loss and compare with baseline audiometry if available. - Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week). - Discontinue suspected agent if this can be done without compromising the regimen. - Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. - Hearing loss is generally not reversible. - The risk of further hearing loss must be weighed against the risk of stopping the injectable in the treatment regimen. - While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.
Visual disturbance/optic neuritis	As per patient's complaint and/or as judged by ophthalmologist.	- Stop the drug. - Refer patient to an ophthalmologist. - Usually reverses with cessation of Ethambutol.
Arthralgia	Pain of the joints as reported by patient and documented by physician, with or without the presence of arthritis.	- Initiate therapy with nonsteroidal anti-inflammatory drugs. - Lower dose of suspected agent if this can be done without compromising regimen. - Discontinue suspected agent if this can be done without compromising regimen. - Symptoms of arthralgia generally diminish over time, even without intervention.
Rash	A dermatologic reaction felt to be related to antituberculosis medications, as documented by physician/dermatologist.	- Stop all antituberculosis drugs. - Reintroduce drug one by one once the rash has subsided.
Peripheral neuropathy	Symptoms and findings consistent with neuropathy, e.g., pain or numbness of the distal extremities or as judged by a physician/neurologist.	- Increase pyridoxine to maximum daily dose (200 mg per day). - Initiate therapy with tricyclic antidepressants, such as amitriptyline. Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. - Lower dose of suspected agent, if this can be done without compromising regimen. - Discontinue suspected agent, if this can be done without compromising regimen. - Patients with comorbid disease (e.g. diabetes, HIV, alcohol neuropathy, or dependence may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here). - Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.
Nephrotoxicity/ renal failure	Elevation of at least one creatinine value >1.4 mg/dl.	- Discontinue suspected agent. - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. - Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). - Adjust all antituberculosis medications according to the creatinine clearance. - History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure. - Renal impairment may be permanent.
Hypothyroidism	At least one measure of TSH > 10.0 IU/ml {normal ranges: TSH (0–10.0 IU/ml)}.	- Initiate thyroxine therapy. - Completely reversible upon discontinuation of PAS or Ethionamide. - The combination of Ethionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.

laboratory investigations were also advised to detect any adverse events. These adverse events were considered only when reflected at least by one abnormal laboratory value confirmed by a repeat test. Few investigations, such as audiometry and ophthalmological evaluations, were advised exclusively whenever clinically indicated. If the patients made any spontaneous complaint, they were interrogated in detail and the necessary actions taken. Adverse events were classified as major if required change in the regimen, i.e. stoppage of offending drug or substitution with another drug.[30] Most of the

adverse events except major ones, such as psychosis, renal failure, and deafness, were managed in the following sequential order, advancing to next step if preceding intervention failed – counseling and symptomatic treatment, splitting of total dose of offending drug, reduction of dose of drug according to lower weight band, permanent discontinuation of drug, and substitution with another drug. Para-aminosalicyclic Acid was a substitute drug for any one bactericidal (Kanamycin, Ofloxacin, Ethionamide, and Pyrazinamide) or two bacteriostatic drugs (Cycloserine and Ethambutol) in case of occurrence of adverse events. Every effort was made not to compromise the whole regimen. Ancillary medicines were also provided for management of adverse events. Patients were also referred to concerned specialist for evaluation and expert opinion if required and even admission for observation, especially for major adverse events.

Data were entered on Microsoft Excel sheet and the accuracy of entry verified against the original paper forms. The data were further checked for any errors and then analyzed using descriptive statistics. Frequencies were used to compare differences in baseline clinical and demographic data between patients experiencing adverse events and those not as well. Absolute frequency counts and measures of central tendency (mean, median) were calculated. Measures of dispersion including range and standard deviation were also calculated. Comparison between groups was performed with the unpaired student *t*-test/nonparametric Mann–Whitney test. All significance tests were two-sided, and a p value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS statistical software 16.0.

The ethical committee of King George Medical University approved the present study.

3. Results

Out of 132 patients, a total of 98 patients proved to be cases of MDR-TB by culture were enrolled for treatment. All the patients were categorized under retreatment cases. 34 patients were excluded from the study (non-MDR susceptibility – 13, more than 1 month treatment of SLDs before diagnosis – 8, migrated/not traced – 3, unwillingness for treatment – 2, major medical/psychiatric illnesses at baseline – 6, and expiry before initiation of treatment – 2). All the patients were found to be HIV negative after testing. Of them, 68 (69.4%) were males and 30 (30.6%) were females. Mean age and weight were 29.3 ± 9.3 years and 42.9 ± 9.1 kg, respectively. Clinical profile of the patients has been illustrated in Table 3. 81 (82.7%) patients completed the treatment while 7 (7.1%) defaulted and 10 (10.2%) died at the completion of treatment. Mean baseline laboratory values (with standard deviations) were as follows: hemoglobin 10.6 ± 4.3 gm/dl, creatinine 1.4 ± 0.8 mg/dl, aspartate aminotransferase (AST) 28.4 ± 14.3 IU/l, alanine aminotransferase (ALT) 32.1 ± 17.9 IU/l, bilirubin 2.6 ± 1.1 mmol/l, potassium 3.3 ± 0.6 mEq/l, and TSH 11.2 ± 8.5 iU/l. None of the patients reported to have deranged laboratory values at baseline. A total of 119 adverse events were observed among this cohort during course of treatment. Most of the adverse events occurred during intensive phase in 77 (78.6%) as compared to that of continuation phase in 42 (42.6%) ($p = 0.02$) patients. 46 (46.9%) patients experienced at least one adverse event. The gastrointestinal adverse events were most commonly observed with a frequency of 48 (40.3%) followed by ototoxicity in 28 (23.6%) among this cohort of 98 patients, as shown in Table 4. The specific gastrointestinal adverse events were nausea/vomiting in 24 (20.2%), anorexia in 9 (7.6%), gastritis in 8 (6.7%), hepatitis in 3 (2.5%), diarrhea in 2 (1.7%), and abdominal pain, as well as constipation, in 1 (0.8%) patient. The specific adverse events related to ototoxicity were deafness in 12 (10.1%), vertigo in 10 (8.4%), and tinnitus in 6 (5.1%) patients. 17 (17.4%) patients had major adverse events requiring drug substitution or permanent discontinuation of

Table 3 – Clinical characteristics of the cohort of 98 patients treated with MDR-TB therapy.

Characteristics	Number (%)
Age (in years)	
≤20	13 (13.3%)
21–30	51 (52.1%)
31–40	24 (24.4%)
≥41	10 (10.2%)
Sex	
Male	68 (69.4%)
Female	30 (30.6%)
Weight (in kg)	
≤30	8 (8.2%)
31–40	33 (33.7%)
41–50	38 (38.8%)
51–60	16 (16.2%)
≥61	3 (3.1%)
Total duration of illness (in years)	
<1	6 (6.1%)
1–2	42 (42.8%)
3–4	38 (38.8%)
>5	12 (12.3%)
Number of episodes of pulmonary tuberculosis for which treatment taken	
Two	54 (55.1%)
Three	30 (30.6%)
More than three	14 (14.3%)
Time lapse between treatment for first and second episodes of pulmonary tuberculosis (in months)	
<6	11 (11.2%)
6–12	35 (35.7%)
13–18	26 (26.5%)
19–24	18 (18.4%)
>24	8 (8.2%)
Time lapse between treatment for second and third episodes of pulmonary tuberculosis (in months)	
<6	9 (9.2%)
6–12	12 (12.2%)
13–18	10 (10.2%)
19–24	7 (7.1%)
>24	6 (6.1%)
Time lapse between treatment for third and subsequent episodes of pulmonary tuberculosis (in months)	
<6	1 (1.1%)
6–12	4 (4.1%)
13–18	6 (6.1%)
19–24	2 (2.1%)
>24	3 (3.1%)
Number of MDR-TB patients experiencing adverse events during treatment	
One adverse event	8 (8.2%)
Two adverse events	11 (11.2%)
More than two adverse events	27 (27.6%)

Table 4 – Frequency of adverse events in both treatment phases and suspected agents among 98 patients receiving MDR-TB treatment in Lucknow, India.

Grouped adverse events	Specific adverse events	Frequency of adverse events	Months of treatment at presentation Median (range)	Adverse events observed during intensive phase	Adverse events observed during continuation phase	Drugs implicated
Gastrointestinal	Nausea/vomiting	24 (20.2%)	3.4 (0.1–26.8)	18 (23.4%)	6 (14.3%)	Eto, Cs, Z, Ofx
	Anorexia	9 (7.6%)	4.4 (0.5–16.5)	7 (9.1%)	2 (4.8%)	Eto
	Gastritis	8 (6.7%)	3.9 (0.7–17.8)	6 (7.8%)	2 (4.8%)	Eto, PAS
	Hepatitis	3 (2.5%)	2.5 (0.5–12.6)	2 (2.6%)	1 (2.4%)	Eto, Z
	Diarrhea	2 (1.7%)	9.1 (6.4–22.7)		2 (4.8%)	Eto, PAS
	Abdominal pain	1 (0.8%)	5.2	1 (1.3%)		Eto, PAS
	Constipation	1 (0.8%)	12.4		1 (2.4%)	Eto
Total		48 (40.3%)		34 (44.2%)	14 (33.5%)	
Ototoxicity	Deafness	12 (10.1%)	6.4 (0.2–25.3)	8 (10.4%)	4 (9.5%)	Km
	Vertigo	10 (8.4%)	5.9 (0.1–20.5)	8 (10.4%)	2 (4.8%)	Km, Cs, Ofx
	Tinnitus	6 (5.1%)	6.1 (0.4–27.2)	4 (5.2%)	2 (4.8%)	Km
Total		28 (23.6%)		20 (26.0%)	8 (19.1%)	
Neurological	Dizziness	10 (8.4%)	5.1 (0.4–22.5)	7 (9.1%)	3 (7.1%)	Km, Cs, Ofx
	Headache	8 (6.7%)	7.7 (0.1–26.3)	4 (5.2%)	4 (9.5%)	Cs, Km
	Peripheral neuropathy	3 (2.5%)	15.3 (9.2–17.8)		3 (7.1%)	Eto, Km, Cs
Total		21 (17.6%)		11 (14.3%)	10 (23.7%)	
Psychiatric	Psychosis	5 (4.2%)	3.8 (1.2–21.8)	1 (1.3%)	4 (9.5%)	Cs
	Depression	1 (0.8%)	13.0		1 (2.4%)	Cs
Total		6 (5.0%)		1 (1.3%)	5 (11.9%)	
Others	Arthralgia	9 (7.6%)	2.7 (0.2–25.4)	8 (10.4%)	1 (2.4%)	Z
	Visual disturbance	3 (2.5%)	10.4 (2.3–14.6)	1 (1.3%)	2 (4.8%)	E, Eto
	Rash	2 (1.7%)	4.4 (0.2–11.3)	2 (2.6%)	0 (0.0%)	Ofx
	Hypothyroidism	1 (0.8%)	7.0		1 (2.4%)	Eto, PAS
	Renal failure	1 (0.8%)	8.0		1 (2.4%)	Km
Total		16 (13.4%)		11 (14.3%)	5 (12.0%)	
Overall adverse events		119 (~100%)		77 (78.6%)	42 (42.6%)	

Abbreviations: E, Ethambutol; Z, Pyrazinamide; Km, Kanamycin; Cs, Cycloserine; Eto, Ethionamide; Ofx, Ofloxacin; PAS, Para-aminosalicylic acid.
Note: Sum of column percentages may exceed 100% because a patient may experience more than one adverse event.

drugs. 7 (7.1%) patients required admission to hospital for occurrence of adverse events. None of the patients had to discontinue their complete regimen permanently due to major adverse events. Deafness and tinnitus leading to withdrawal of injectable was most frequent in 5 (5.1%) followed by psychosis in 4 (4.1%), gastrointestinal intolerance in 3 (3.1%), and arthralgia together with hepatitis in 4 (4.1%), as mentioned in Table 5. All patients in our study with major adverse events, such as deafness, renal failure, and hepatitis, were found to have deranged laboratory parameters supporting in addition to diagnosis based on clinical examination. The offending drugs responsible for these major adverse events were injectable Kanamycin (deafness/renal failure), Cycloserine (psychosis), Ethionamide (gastrointestinal tolerance), and Pyrazinamide (arthralgia/hepatitis). No mortality occurred due to major adverse events in our cohort. The causes for mortality among

Table 5 – Frequency of major adverse events and suspected agents among 98 patients receiving MDR-TB treatment in Lucknow, India.

Agents	Specific major adverse events observed	Number of patients experiencing major adverse events	Months treatment at presentation Median (range)	Number of patients requiring substitution with other drug	Number of patients requiring discontinuation of drugs
Kanamycin	Deafness	4 (4.1%)	5.2 (0.4–24.1)	1	3
	Tinnitus	1 (1.1%)	6.5 (1.2–21.5)	1	0
Cycloserine	Renal failure	1 (1.1%)	8.0 (0.0–8.0)	0	1
	Psychosis	4 (4.1%)	4.2 (1.2–19.5)	0	4
Pyrazinamide	Arthralgia	2 (2.1%)	3.8 (0.3–21.4)	1	1
	Hepatitis	2 (2.1%)	4.5 (0.2–23.2)	1	1
Ethionamide	Nausea	1 (1.1%)	2.2 (0.1–26.3)	1	0
	Vomiting	1 (1.1%)	1.4 (0.2–25.2)	1	0
	Hypothyroidism	1 (1.1%)	7.0 (0.0–7.0)	0	1
Total		17/98 (17.4%)			

Table 6 – Demographic and clinical characteristics of patients with and without adverse events.

Characteristics	Patients with adverse events ($n = 46$)	Patients without adverse events ($n = 52$)	p value
Mean age (in years)	32.5 ± 11.9	28.4 ± 8.2	0.10
Sex (male)	30	28	0.28
History of alcohol intake	18 (39.1%)	13 (25.0%)	0.19
History of drug addiction	9 (19.6%)	8 (15.4%)	0.61
Diabetes mellitus	6 (13.1%)	5 (9.6%)	0.75
Total duration of illness (in years)	4.7 ± 3.5	4.9 ± 3.7	0.82
Mean sputum conversion (in months)	3.8 ± 1.6	2.8 ± 2.6	0.23
Mean culture conversion (in months)	4.1 ± 2.5	3.1 ± 3.9	0.15
Extent of lesions on chest X-ray			
Unilateral	18 (39.1%)	29 (55.8%)	0.11
Bilateral	28 (60.9%)	23 (44.2%)	
Outcome			0.38
Defaulted	3 (6.5%)	4 (7.7%)	0.41
Expired	5 (10.9%)	5 (9.6%)	0.43
Failure	4 (8.7%)	6 (11.5%)	0.34
Cured	34 (73.9%)	37 (71.6%)	0.45

ten patients were found to be acute respiratory failure due to extensive disease (4), accidental trauma (2), viral hemorrhagic fever with multiorgan failure (2), acute coronary syndrome (1), and complicated malaria (1). All the adverse events were reversible either with supplementary/ancillary medications or withholding the suspected offending agents, except deafness that was permanent on repeated audiometry. Patients who experienced adverse events were older ($p = 0.10$), predominantly males ($p = 0.28$), had higher incidence of alcoholism ($p = 0.19$), and drug addiction ($p = 0.61$), as compared to those having no adverse events, but these differences were not significant on univariate analysis, as mentioned in Table 6. No significant differences were observed between these two groups regarding default ($p = 0.41$), death ($p = 0.43$), and failure rate ($p = 0.34$). Overall, there was no significant difference in treatment outcome ($p = 0.38$).

4. Discussion

The management of MDR-TB patients has been considered to be complicated, with challenging reasons being prolonged duration of 24–27 months and high toxicity profile of SLDs. Adverse events were experienced by 46 (46.9%) of the patients included in this study mostly in the intensive phase of treatment of MDR-TB. The prevalence of adverse events observed in the current study is lower than the range as reported in other studies, where it ranged from 69% to 96%.[6–27] The reasons for the difference in the prevalence of adverse events across the various studies might be related to several possible factors, such as variation in demographic profiles of cohorts of patients, differences in definitions of adverse events' terminologies, as adopted by physicians, whether the adverse event was reported by patient (subjective) or detected by clinician (objective), on the basis of clinical evidence along with feasibility of monitoring with serial laboratory investigations, whether all or only the major adverse events were studied, the differences in comorbidities, such as diabetes and other covariates including HIV coinfection and variations in the use of specific antitubercular drugs including dosage and also pharmacological interactions with other group of drugs comprising antiretroviral, oral hypoglycemic agents in case of diabetics, and also ancillary medications used for management of adverse events. The observed frequency of specific gastrointestinal events in our study has been found to be in the reported range of 0.5–100% as per the existing literature.[7,9–11,13,17,18,22,25,27] The high prevalence of gastrointestinal adverse events was probably due to frequent reporting by patients as compared to other adverse events leading to subjective variation. The second most common adverse event was ototoxicity reported with a frequency of 28 (23.6%) among this cohort, which exist in the range of 12–70% from the review of the literature.[10,11,17,20,22] The frequency of tinnitus in the present study was within the range of 5–45%, as reported in various studies[9,13,18,22] while that of deafness was within the range of 6.7–33%, as reported in the literature.[6,7,13,18,20,22] There can be a probability of underreporting of ototoxicity by patients in our study, while some studies have reported higher rates of ototoxicity.[20,22] The reason for that was that there were no routine audiometry assessments conducted throughout the treatment. Ototoxicity is predominantly associated with the use of injectable aminoglycoside (Kanamycin), although there is possibility of additive effects of interaction with other concomitant and potentially ototoxic drugs that were used in the regimen, such as Ofloxacin and Cycloserine. This warrants further investigation to uncover the possibility of these interactive effects. In our study, adverse events were major and were requiring stoppage and/or substitution of the suspected offending drug in 17 (17.4%) of the patients. This prevalence of major adverse events is lower than that reported in the literature,[6,9,15,18,25,31] but found to be higher than the prevalence of 11.7% and 15%, as reported by Furin et al. and Sagwa et al., respectively.[7,22] This may be due to early identification and aggressive management strategies adopted by DOTS PLUS programme. However, our findings are almost similar to that of Singla et al. and Yew et al., which reported prevalence of 18% and 19%, respectively.[24,32] Baghaei et al. reported deafness and headache/psychosis occurring due to injectable Kanamycin and Cycloserine, respectively, and were found to be major adverse events

that required frequent discontinuation and/or substitution.[20] Our study also reported similar findings. MDR-TB patients should be managed aggressively for adverse events during therapy, especially for ototoxicity and psychiatric disorders.

There are several limitations in our current study. The major limitation was that routine monitoring was not performed despite the prospective nature of our study. The adverse events recorded on the chart were based predominantly on clinical evidence, particularly on the basis of patient-reported symptoms. There was a possibility of selective underreporting of adverse events by patients or the selective recording of adverse events by clinicians. Patients might not have reported some adverse events, such as gastrointestinal, depression, arthralgia, and headache, unless these were serious, as leading questions were not asked. Some occult adverse events, such as asymptomatic hepatitis, nephrotoxicity, hearing loss in high frequency range, and hypothyroidism, may not be detected, and therefore are not reported without routine monitoring. There could be the possibility of underestimation of these adverse events in our case due to the fact that frequent monitoring with laboratory investigations was not performed because of financial constraints in this resource-limited setting and also patients with serious illnesses were excluded. The younger age of the patients in this study may also have led to the lower proportion of adverse drug events as compared to other published data, as the impact of comorbidities associated with older age groups could not be captured. Patient with comorbidities can have higher frequency of adverse events, as these patients are on drugs other than antitubercular therapy, and regimen can also be modified as in kidney or liver failure. These patients were excluded in our study as per RNTCP protocol leading to variation in frequency, as compared to other studies. The mortality might have been due to adverse events, given the lack of routine monitoring, although responsible causes were sorted out. These factors might have confounded to biasing of the results leading to deviation from the true prevalence.

This study found that 46 (46.4%) patients experienced at least one adverse event. 17 (17.4%) patients reported major adverse events. Despite major adverse events, 81 (82.7%) patients completed the therapy with the cure rate of 71 (72.4%). Adverse events can be detected by clinical evidence in resource-limited settings.

Author contributions

Dr. Abhijeet Singh, along with Dr. Rahul Srivastava and Dr. Giridhar B. Hosmane, has worked for the cases including recording of data.

Dr. Rajendra Prasad, along with Dr. RAS Kushwaha and Dr. Amita Jain, have collectively contributed in the form of valuable intellectual inputs in the diagnosis and management of case.

Conflicts of interest

The authors have none to declare.

REFERENCES

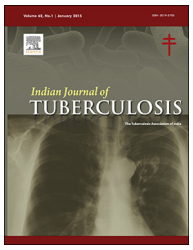
1. *World Health Organization Global Tuberculosis Report 2012. WHO/HTM/TB/2012.6*. Geneva, Switzerland: WHO; 2012.
2. Caminero JA. Treatment of MDR-TB: evidence and controversies. *Int J Tuberc Lung Dis*. 2006;10:829–837.
3. Farmer PE, Furin JJ, Shin SS. Managing MDR-TB. *J Respir Dis*. 2000;21:53–56.
4. Farmer PE, Kim KY, Mitnick CD, Timperi R. Responding to outbreaks of MDR-TB: introducing DOTS-PLUS. In: Reichman L, Hershfield ES, eds. In: *Tuberculosis: A Comprehensive International Approach* 2nd ed. NY, USA: Marcel Dekker; 2000 :447–469.
5. World Health Organization Guidelines for establishing DOTS-PLUS pilot projects for the management of MDR-TB. Gupta R, Arnadottir T, eds. In: *WHO/CDS/TB/2000.279*. Geneva, Switzerland: WHO; 2000.
6. Tahaoglu K, Torun T, Sevim T, et al. The treatment of MDR-TB in Turkey. *N Engl J Med*. 2001;345:170–174.
7. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for MDR-TB. *Int J Tuberc Lung Dis*. 2001;5:648–655.
8. Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of MDR-TB. *CMAJ*. 2002;167:131–136.
9. Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of MDR-TB: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis*. 2005;9:1027–1033.
10. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualized treatment of MDR-TB in Latvia: a retrospective cohort study. *Lancet*. 2005;365:318–326.
11. Törün T, Güngör G, Özmen I, et al. Side effects associated with the treatment of MDR-TB. *Int J Tuberc Lung Dis*. 2005;9:1373–1377.
12. Nahar BL, Mosharrof Hossain AKM, Islam MM, Saha DR. A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period. *Bangladesh J Pharmacol*. 2006;1:51–57.
13. Tupasi TE, Gupta R, Quelapio MID, et al. Feasibility and cost-effectiveness of treating MDR-TB: a cohort study in the Philippines. *PLoS ONE*. 2006;3:e352. http://dx.doi.org/10.1371/journal.pmed.0030352.
14. Cox HS, Kalon S, Allamuratova S, et al. MDR-TB treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. *PLoS ONE*. 2007;2.e1126. http://dx.doi.org/10.1371/journal.pone.0001126.
15. Shin SS, Pasechnikov AD, Gelmanova IY, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. *Int J Tuberc Lung Dis*. 2007;11:1314–1320.
16. Lanternier F, Dalban C, Perez L, Bricaire F, Costagliola D, Caumes E. Tolerability of anti-tuberculosis treatment and HIV sero-status. *Int J Tuberc Lung Dis*. 2007;11:1203–1209.
17. Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer PE, Satti H. Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. *PLoS ONE*. 2009;4:e7186. http://dx.doi.org/10.1371/journal.pone.0007186.
18. Bloss E, Kukša L, Holtz TH, et al. Adverse events related to MDR-TB treatment, Latvia, 2000–2004. *Int J Tuberc Lung Dis*. 2010;14:275–281.
19. Palmero D, Cruz V, Museli T, Pavlovsky H, Fernandez J, Waisman J. Adverse drug reactions in MDR-TB. *Medicina (B Aires)*. 2010;70:427–433.
20. Baghaei P, Tabarsi P, Dorriz D, et al. Adverse effects of MDR-TB treatment with a standardized regimen: a report from

Iran. *Am J Ther*. 2011;18:e29–e34. http://dx.doi.org/10.1097/MJT.0b013e3181c0806d.
21. Carroll MW, Lee M, Cai Y, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. *Int J Tuberc Lung Dis*. 2012;167:961–966. http://dx.doi.org/10.5588/ijtld.11.0574.
22. Sagwa E, Mantel-Teeuwisse AK, Ruswa N, et al. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *South Med Rev*. 2012;5:6–13.
23. Van der Walt M, Lancaster J, Odendaal R, Davis JG, Shean K. Serious treatment related adverse drug reactions amongst anti-retroviral naive MDR-TB patients. *PLOS ONE*. 2013;8:e58817. http://dx.doi.org/10.1371/journal.pone.0058817.
24. Singla R, Sarin R, Khalid UK, Mathuria K, Singla N. Seven-year DOTS-Plus pilot experience in India: results, constraints and issues. *Int J Tuberc Lung Dis*. 2009;13:976–981.
25. Joseph P, Desai VB, Mohan NS, Fredrick JS, Ramachandran R. Outcome of standardized treatment for patients with MDR-TB from Tamil Nadu, India. *Indian J Med Res*. 2011;133:529–534.
26. Saakidis P, Cox HS, Varghese B, Montaldo C, Da Silva E. Ambulatory MDR-TB treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. *PLoS ONE*. 2011;6:e28066.
27. Isaakidis P, Varghese B, Mansoor H, Cox HS, Ladomirska J. Adverse events among HIV/MDR-TB co-infected patients receiving antiretroviral and second line anti-TB treatment in Mumbai, India. *PLoS ONE*. 2012;7:e40781. http://dx.doi.org/10.1371/journal.pone.0040781.
28. Ministry of Health and Family Welfare. Central TB Division. DGHS. *Revised National Tuberculosis Control Programme Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) in India*. MOHFW India; 2010.
29. World Health Organization. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Emergency Update 2008. WHO/HTM/TB/2008.402*. Geneva, Switzerland: WHO; 2008.
30. Serena Koenig Management of Side Effects during MDR-TB Treatment; TB CARE II project, United States Agency for International Development.
31. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh Jr CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
32. Yew WW, Chan CK, Chau CH, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with Ofloxacin/levofloxacin-containing regimens. *Chest*. 2000;117:744–751.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original Article

Lung health and heart rate variability changes in salt workers

M.I. Glad Mohesh [a,*], A. Sundaramurthy [b]

[a] Assistant Professor, Department of Physiology, Shri Sathya Sai Medical College & Research Institute, Ammapettai, Kancheepuram District, 603108, Tamilnadu, India

[b] Department of Pulmonary Medicine, Shri Sathya Sai Medical College & Research Institute, Ammapettai, Kancheepuram District, 603108, Tamilnadu, India

ARTICLE INFO

Article history:
Received 31 December 2014
Accepted 9 July 2015
Available online 7 December 2015

Keywords:
Salt workers
Heart rate variability
Plasma electrolytes

ABSTRACT

Background: India is the third largest salt producing country in the World, with a global annual production of 230 million tonnes. Large number of salt workers get employed in these salt milling plants risking their life from the effects of salt. Recent foreign evidences reported that these salt workers are exposed to aerosol salt particles that disturb their lung and cardiovascular autonomic control.

Objectives: To compare the status of lung health, cardiovascular autonomic control and biochemical changes in a group of salt industry workers with that of the age-matched normal subjects.

Methodology: Volunteers of both sexes (25–35 years) were divided into Group I ($n = 10$) controls and Group II ($n = 10$) non-brine salt workers in salt milling plants. From fasting blood sample, complete blood count, plasma electrolyte and lipid profile estimation were done. After resting for 15 min, blood pressure and lead II ECG were recorded. Spirometry was done using RMS Helios spirometer. Data collected were later analysed using GraphPad Prism 5.0 with statistical significance set at $p < 0.05$.

Results: Blood pressure recorded showed a slight elevation in the subjects than that in the controls. Significant rise of plasma sodium (141.9 ± 0.4, 138.7 ± 1.0, $p < 0.008$) and chloride (113.9 ± 1.3, 107.7 ± 1.4, $p < 0.005$). Spirometric tests showed mild obstructive airway disease in the subjects with FEV_1 and FEV_1/FVC significantly lower than the controls (81.11 ± 3.8, 92.0 ± 3.3, $p < 0.049$), (37.4 ± 4.0, 112.8 ± 1.7, $p < 0.0001$), $FEF_{25-75\%}$ (123.3 ± 5.6, 101.0 ± 5.6, $p < 0.01$). Heart rate variability parameters also showed statistically significant variation.

Conclusion: Exposure to salt aerosols by the workers in the salt industry has shown a little or no impact on the respiratory system, however there are changes in the blood and cardiovascular system, which need to be further studied to understand the long-term influences of salt in this population.

* *Corresponding author.* Tel.: +91 044 27440346.
E-mail address: gladmohesh@gmail.com (M.I. Glad Mohesh).

http://dx.doi.org/10.1016/j.ijtb.2015.07.002

1. Background

Salt milling industries were seen across the coastal India. We are the third largest salt producing country in the world, with global annual production of 230 million tonnes.[1] Large number of salt workers do get employed in these salt milling plants risking their life from the effects of salt. Very less studies have been done on these workers on their lung health and cardiac autonomic health status. In Tamilnadu, the districts of Kancheepuram, Cuddalore, Nagapattinam, Ramanathapuram, Kanniyakumari and Tuticorin are well known for their salt pans and salt milling plants. All evidences to prove the association between dietary salt and hypertension are available, and also studies that showcases if the intake of sodium is lowered in these hypertensive's, the possible extent of lowering blood pressure that could be achieved are also documented.[2] A study on the influence of dietary salts' role on hypertension in Dahl rats has mapped the sympathetic neural mechanism's role of afferent baroreceptors, central neural and peripheral adrenergic mechanisms. This study has proved the role of altered sympathetic on salt induced hypertension.[3] Inhaled respiratory irritants such as chlorine can cause chronic airway disease was highlighted.[4] Harbour workers are exposed to the salt aerosols coming directly from the sea, in whom the existence of arterial hypertension is of a serious concern.[5] Authors from India in their study have concluded that inhalation of salt particles by workers in the non-brine areas of the salt milling plants results in increased blood pressure. They have suggested these,

1. Salt particles may be inhaled and can be absorbed in the airway surface of epithelium.
2. Inhaled salt particles may be carried away from the lungs into the blood.
3. Inhaled salt particles may be even carried by the upward mucociliary current to the throat, where they can be swallowed. This in turn could increase the blood pressure and also increases the risk of hypertension in these salt workers.[6] It was also reported that, other than the regular ophthalmic, dermatological and joint problems, prevalence of hypertension was about 12% among the salt workers.[7] Recently some authors have explained how aerosols from sea would contribute significantly to the tropospheric chloride content. This in turn would be available in the atmosphere as an irritant for the lung to cause lung diseases.[8] With more evidences to say that salt workers are exposed to aerosol salt particles, and hence their lung and cardiovascular autonomic control is getting affected, here in this study we used the following testing methods to understand our objectives mentioned below: (a) Spirometry is a standard test to understand, if someone is suffering from obstructive or restrictive lung disease. With the ease of non-invasive approach, the subject's lung health can be assessed. (b) Short-term heart rate variability is an advanced derivative of the 5 min lead II ECG acquired from a subject to record and analyse his cardiovascular autonomic derangements. Biochemical parameters such as plasma sodium, potassium and chloride content can help us in estimating the elevated levels if any.

2. Objectives

To compare the status of lung function, cardiovascular autonomic control status and plasma electrolyte changes in a group of salt workers and age matched normal subjects.

3. Materials and methods

This study was started after getting permission from the Institutional Ethics Committee. Convenience sampling of subjects who were working in salt milling plants for a period of 1 year and between 25 and 35 years of age were included in the study (Group II, $n = 10$). Age matched subjects who do not work in salt milling plant served as controls (Group I, $n = 10$). Smokers, alcoholics and persons with chronic illness or medications for any illness are excluded from the study. Subjects were asked to come to the Medical College Hospital on a particular day and time after fasting overnight between 7 and 8 am. 5 ml of blood was taken in the central lab of the hospital under sterile conditions to estimate the plasma sodium, potassium and chloride. After that, subjects were allowed to take breakfast (given free) with no caffeinated drinks. They were taken to Physiology research lab to record anthropometric data such as height and weight using a fixed stadiometer and Krups weighing machine. After 15 min of supine resting, blood pressure was measured using OMRON HEM 4021 semiautomatic digital sphygmomanometer. Lead II ECG recording was made after the stabilisation of respiratory rate to around 12–18 breaths/min (RMS Polyrite). With the stabilised ECG wave a 5 min continuous ECG recording was made and data were stored in a database (computer) for analysis. Lung function testing was done using RMS Helios 401 spirometer; three attempts were made on each recording. Graphs were checked for acceptability and reproducibility. Printouts of the results were obtained and stored. Following analysis on the data collected was done: (1) Blood pressure (systolic/diastolic) was used to calculate MABP and pulse pressure. (2) Spirometric results to find whether the lung functions are normal/obstructive/restrictive. (3) Interbeat intervals picked up from the 5 min lead II ECG recording were used to derive the various HRV variability measures using Kubios HRV software v 2.1. (4) Biochemical test results from the lab gave an estimation of plasma sodium, potassium and chloride. Statistical significance of the data collected was analysed using Student ''t'' test using GraphPad Prism software with significance set at $p < 0.05$.

4. Results

Our study aimed at the occupational hazards the workers of the salt milling plants who are exposed to a high amount of salt aerosol in the air. Table 1 explains the anthropometric details of the participants. Table 2 showcases the differences

in the blood pressure parameters and the biochemical parameters estimated. Significant changes were noted in the systolic blood pressure (SBP) and heart rate of the study subjects. Also an important feature to note is the rise in the plasma electrolyte in these people which significantly can land them in diseases of cardiovascular system including hypertension, CVD, etc.

Lung function tests made on the subjects through spirometry revealed a significant decrease in the FEV_1 and FEV_1/FVC parameters which offer a possibility of these subjects suffering from the mild obstructive lung disease (Table 3).

Cardiovascular autonomic control assessment through heart rate variability measures on both the time domain and frequency domain measures showed a low value of both sympathetic and parasympathetic power of control when compared to the control subjects who are age matched subjects. There are statistically significant changes seen in the existing cardiovascular autonomic control parameters between the two groups (Table 4).

Table 1 – Anthropometric details of the subjects.

	Control ($n = 10$)	Study ($n = 10$)	p value
Age (years)	28.40 ± 1.09	29.80 ± 1.15	0.3907
Height (cm)	166.5 ± 1.44	161.7 ± 1.45	0.0325*
Weight (kg)	70.11 ± 3.75	64.40 ± 1.32	0.1685
BMI	25.36 ± 1.44	24.67 ± 0.61	0.6624

* $p < 0.05$.

Table 2 – Comparison of blood pressure and plasma electrolyte levels in the salt workers ($n = 10$) and in the control subjects ($n = 10$).

	Control	Study	p value
SBP (mmHg)	123.4 ± 2.45	130.2 ± 2.13	0.0499*
DBP (mmHg)	75.90 ± 2.26	82.50 ± 2.51	0.0672
PP (mmHg)	47.45 ± 2.13	47.70 ± 2.26	0.9368
MABP (mmHg)	91.56 ± 2.10	98.24 ± 2.15	0.0395*
Heart rate (beats/min)	66.30 ± 6.65	88.60 ± 1.07	0.0039*
Na^+	138.7 ± 1.001	141.9 ± 0.40	0.0083*
K^+	4.050 ± 0.083	3.63 ± 0.035	0.0002*
Cl^-	107.7 ± 1.48	113.9 ± 1.303	0.0057*

* $p < 0.05$.

Table 3 – Comparison of spirometric changes seen in the study subjects ($n = 10$) and in the controls ($n = 10$).

	Control	Study	p value
FEV_1 (% predicted)	92.0 ± 3.38	81.11 ± 3.83	0.0490*
FVC (% predicted)	81.56 ± 3.42	83.56 ± 6.94	0.7990
FEV_1/FVC	112.8 ± 1.77	37.44 ± 4.05	0.0001*
$FEF_{25-75\%}$ (L/s)	101.0 ± 5.6	123.3 ± 5.64	0.0126*
PEFR (L/s)	82.11 ± 4.26	81.89 ± 4.27	0.9711

* $p < 0.05$.

Table 4 – Comparison of the short-term heart rate variability parameters between the control subjects ($n = 10$) and the salt workers ($n = 10$).

Parameters	Control	Study	p value
Mean RR (ms)	824.40 ± 23.15	691.40 ± 19.31	0.0125*
SDNN (ms)	27.53 ± 02.80	18.97 ± 00.77	0.1339
pNN50[a]	16.32 ± 01.15	00.66 ± 00.24	0.0001*
RMSSD (ms)	32.69 ± 02.84	19.27 ± 01.35	0.0303*
VLF power (ms^2)	54.40 ± 07.64	22.33 ± 01.45	0.0480*
LF power (ms^2)	554.60 ± 128.0	115.70 ± 26.67	0.0962
HF power (ms^2)	300.80 ± 57.43	39.33 ± 01.76	0.0341*
Total power (ms^2)	904.20 ± 162.9	180.00 ± 27.84	0.0379*
LF (nu)	59.59 ± 03.52	66.20 ± 03.23	0.3530
HF (nu)	36.34 ± 03.62	20.40 ± 02.41	0.0419*
LF/HF ratio	1.99 ± 00.47	03.27 ± 00.51	0.1980

[a] Number of successive RR interval pairs that differ more than 50 ms divided by total number of RR intervals.
* $p < 0.05$.

5. Discussion

We compared the various parameters such as respiratory, cardiovascular and biochemical of salt workers with that of the age matched control subjects. Salt in the form of aerosols in the salt milling plants and salt farms is a source of causative agent for salt induced hypertension and other problems. This has reflected in a significant increase in the blood pressure and heart rate of these salt workers. The increased mean plasma levels of sodium and chloride denote the possibility of the salt aerosol entry into the circulation of the workers who are exposed to the salt aerosols in the workplace in which the only mode of entry could be the air they breath.[6]

The significant decrease in FEV_1 (% predicted) values in the study subjects denotes an overall mild decrease in the forced expiratory volume of the lung, however it is difficult to conclude if the subjects are suffering from any obstructive pulmonary disease as the values are >80% of the predicted. FVC (% predicted) is found to be >80% predicted in both the groups, and hence restrictive disease is not to be suspected. An FEV_1/FVC of <70% is diagnostic of air flow obstruction and confirms obstructive disease. Also FEV_1 does not have to be <80% predicted for a diagnosis of airflow obstruction. Here, in our study the results showed a decrease as <70% of the FEV_1/FVC ratio (37.44 ± 4.05), for which a diagnosis of COPD can be made only with the presence of respiratory symptoms such as breathlessness or cough which could be classified as mild COPD.[9] Our subjects did not complain any breathlessness or cough and hence cannot be concluded as mild COPD. Influence of salt aerosols on respiratory system is less although the lungs serve the route of entry of the salt from air.

The lowered mean RR interval denotes an increased overall heart rate in these subjects. Sympathovagal balance is denoted by the mean RR interval. Results suggest that the sympathetic activity of the heart to be high in these subjects. A fall in the SDNN (standard deviation of time interval between consecutive R peaks resulting from sinus node depolarisation) and the total power of the subjects in comparison to that of the

controls suggest that there is a total decrease in the HRV. Reason could be the excessive salt overload in the blood. A very low fall in the HF power (high frequency) that points to a decrease in the parasympathetic activity with a high sympathetic activity in place supported by the increase in blood pressure could lead to morbidity due to cardiovascular problems that could arise early in the lives of these workers associated with other factors such as ageing, atherosclerosis, diabetes, obesity, smoking and alcoholism. Total power of the spectral analysis showed a remarkably low value in comparison to the controls which is of concern as the fall in the regulatory effect on the heart is loosened which could lead to disaster if left uncontrolled. RMSSD (root-mean square of the difference between two adjacent R-R intervals) is a better parameter to express the changes in resting HRV and also is highly reproducible.[10] Low values of RMSSD than the controls is of real concern which shows the loss of parasympathetic control over the heart. LF/HF ratio is a surrogate for understanding sympathovagal tone. Our results showed a greater value of LF/HF ratio in the salt workers than in the controls suggesting a higher sympathetic activity than the parasympathetic or vagal activity.

Our study shows a clear reduction in both the time and frequency domain measures of the total heart rate variability in these salt workers. Lesser the variability greater is the chance for cardiovascular morbidity and mortality.[11]

6. Conclusion

In this study, we found that salt workers working in salt milling plants are more prone for an increase in plasma electrolytes resulting with increased blood pressure and lowered cardiovascular autonomic control. The effect of salt on the various systems on their body of these workers needs to be studied more to understand the extent of potential damage the salt aerosols can do in these subjects. The results suggest these salt aerosols could be considered as a silent killer that should be taken into account in the employment of workers in these industries. Masks of high quality to prevent inhaling directly the salt loaded air and regular health checkups with intervals in the employment could help these subjects to earn a livelihood by working in these industries without harming themselves.

7. Limitations of the study

1. Sample size was too small to conclude effectively.
2. Large-scale studies of COHORT type could reveal the health problems with a clear picture.
3. Studies if conducted across the country could definitely bring a good picture of the problem these workers are facing with.
4. Radiological examination and the assessment of particle size of the suspended salt aerosols were not done.

Authors' contribution

M.I. Glad Mohesh, B.P.T., M.Sc., Ph.D. (a) Conception or design of the work, (b) acquisition, analysis, & interpretation of data for the work, (c) drafting the work or revising it critically for important intellectual content and (d) final approval of the version to be published.

Dr. A. Sundaramurthy, MBBS, MD. (a) Drafting the work or revising it critically for important intellectual content, (b) conception or design of the work and (c) final approval of the version to be published

Conflicts of interest

The authors have none to declare.

Acknowledgement

Authors thank the Tuberculosis Association of India, New Delhi for funding this project.

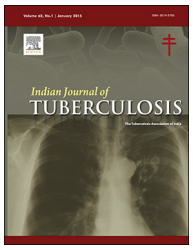
REFERENCES

1. http://saltcomindia.gov.in/industry_india.html.
2. Louis Tobian Jr MD. Dietary salt (sodium) and hypertension. *Am J Clin Nutr*. 1979;32:2659–2662.
3. Mark AL. Sympathetic neural contribution to salt-induced hypertension in Dahl rats. *Hypertension*. 1991;17(suppl I):I-86–I-90.
4. Newman Taylor AJ. Respiratory irritants encountered at work. *Thorax*. 1996;51:541–545.
5. Skrobonja A, Kontosic I. Arterial hypertension in correlation with age and body mass index in some occupational groups in the harbour of Rijeka, Croatia. *Ind Health*. 1998;36:312–317.
6. Haldiya KR, Mathur ML, Sachdev R, Saiyed HN. Risk of high blood pressure in salt workers working near salt milling plants: a cross-sectional and interventional study. *Environ Health*. 2005;4:13.
7. Sachdev R, Mathur ML, Haldiya KR, Saiyed HN. Work related health problems in salt workers of Rajasthan, India. *Indian J Occup Environ Med*. 2006;10(2):62–64.
8. Thornton JA, Kercher JP, Riedel TP, Wagner NL, Cozic J, Holloway J. A large atomic chlorine source inferred from mid-continental reactive nitrogen chemistry. *Nature*. 2010;464(11):271–274.
9. NICE. *Management of Chronic Obstructive Pulmonary Disease: Management of Adults in Primary and Secondary Care*. London: NICE; 2010 www.nice.org.uk/CG101.
10. Task Force of The European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Eur Heart J*. 1996;17:354–381.
11. Huikuri HV, Makikallio RH. Heart rate variability in ischemic heart disease. *Auton Neurosci Basic Clin*. 2001;90:95–101.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Short Communication

Drug susceptibility testing of rapidly growing mycobacteria in extrapulmonary tuberculosis

Geeta V. Gole *, *Reena Set*, *Nishat Khan*, *Jayanthi Shastri*

Department of Microbiology, T.N. Medical College & B.Y.L. Nair Ch. Hospital, Mumbai 08, India

ARTICLE INFO

Article history:
Received 4 May 2015
Accepted 19 April 2016
Available online 15 June 2016

Keywords:
M. chelonae–abscessus group
M. fortuitum
M. smegmatis

ABSTRACT

There has been an increasing awareness of the rapidly growing mycobacteria (RGM), of which numerous species and phylogenetic groups are clearly established human pathogens. It is important to appropriately distinguish RGM from other mycobacteria, as first-line antituberculous drugs are ineffective for their treatment. Variability in susceptibility of RGM is seen in relation to species, different geographical areas, and time. Therefore, we conducted a study to speciate the isolates of RGM and perform antimicrobial susceptibility testing.

The study was carried out in the department of microbiology of a tertiary care hospital. This study included 40 isolates of RGM obtained from clinical specimens from suspected cases of extrapulmonary tuberculosis. Forty isolates of RGM were speciated by phenotypic methods and drug susceptibility testing was done by broth microdilution method.

Of the 40 isolates of RGM, 55% belonged to *Mycobacterium fortuitum* group, 35% were *M. smegmatis* group, and 10% were *M. chelonae–abscessus* group. In *M. fortuitum* group, sensitivity was seen to amikacin (13.63%), cefoxitin (18.18%), imipenem (31.81%), ceftriaxone (22.72%), and cotrimoxazole (31.81%). Only 14.28% and 7.14% of *M. smegmatis* were sensitive to cotrimoxazole and amikacin, respectively. *M. chelonae–abscessus* group was resistant to all the antibiotics tested and showed only intermediate sensitivity to amoxicillin–clavulanic acid (50%) and gatifloxacin (25%).

A variability in sensitivity to different antimicrobials exists in all groups. Hence, it is advisable to perform antimicrobial susceptibility test before commencement of therapy.

1. Introduction

Rapidly growing mycobacteria (RGM) cause a variety of infections. The species of RGM producing disease in humans consist primarily of the *Mycobacterium fortuitum* group, the *M. chelonae/abscessus* group, and the *M. smegmatis* group. A recent study in India showed that 36% of all nontuberculous mycobacterial infections were RGM.[1] RGM should be distinguished from others, as conventional antituberculous drugs are ineffective for RGM infections. Therefore, we conducted a study to speciate the isolates of RGM and perform antimicrobial susceptibility testing.

2. Methods

The study was conducted in the department of microbiology of a tertiary care hospital after approval from the institutional ethics committee. This study included 40 rapidly growing

* *Corresponding author*. Tel.: +91 9004661749/0251 2474439.
E-mail address: dr.geetagole@rediffmail.com (G.V. Gole).

http://dx.doi.org/10.1016/j.ijtb.2016.04.001

mycobacterial isolates obtained from clinical specimens from suspected cases of extrapulmonary tuberculosis (EPTB) over a period of 1 year from April 2010 to March 2011. Aseptic collection of body fluids, pus, and lymph nodes was done by needle aspiration and that of tissue specimens by surgical procedures. The urine specimens included in the study were early morning midstream samples collected by the patients in sterile containers on three consecutive days after periurethral cleaning and submitted to the laboratory. The specimens were decontaminated using NALC NaOH (N-acetyl-L-cysteine-sodium hydroxide) method and were inoculated on Lowenstein–Jensen media. Any growth appearing within 1 week was confirmed to be acid-fast bacilli by Ziehl–Neelsen stain and was further characterized by 3-day arylsulfatase test, growth on Mac Conkey's agar without crystal violet, 5% NaCl tolerance test, and nitrate reduction test.[2] For the urine specimens, at least two specimens from one patient yielding the same isolate were included in the study. Antimicrobial susceptibility test was performed by broth microdilution method, which is recommended by CLSI using Sensititre CA MHBT (Trivitron Diagnostics Pvt. Ltd.). Microtitre plates, which were dosed with following antibiotics: linezolid, clarithromycin, amikacin, cefoxitin, ceftriaxone, imipenem, minocycline, tobramycin, ciprofloxacin, gatifloxacin, amoxicillin/clavulanic acid and trimethoprim/sulfamethoxazole, and minimum inhibitory concentrations (MICs) were interpreted as per CLSI guidelines.[3]

3. Results

Forty isolates of RGM from clinically suspected cases of EPTB included in the study were obtained from pus (50%), fine-needle aspirates (FNAC) (22.5%), fluids (12.5%), tissue (7.5%), and urine (7.5%). Of these, 22 isolates (55%) belonged to *M. fortuitum* group, which was the predominant group, followed by 14 isolates (35%) of *M. smegmatis* group. The antimicrobial susceptibility results of all three groups of RGM are depicted in Table 1.

4. Discussion

Amongst the 40 isolates studied, *M. fortuitum* group was the commonest comprising 55% of the RGM isolates, 35% belonged to *M. smegmatis* group, and 10% were *M. chelonae–abscessus* group. In a study by Shenai S, 43.75% of the RGM isolated were *M. fortuitum* and 56.25% were *M. abscessus*.[1] In a study from Taiwan, 34.5% were *M. fortuitum*, 46% were *M. abscessus*, and 19.5% were *M. chelonae*.[4] However, these studies also included pulmonary specimens unlike our study. Moreover, in the present study, *M. smegmatis* group included other arylsulfatase-negative species like *M. vaccae*, *M. thermoresistible*, and *M. flavescens*. The isolates were not subjected to sequence analysis, which has been the limitation of our study; hence, many of the arylsulfatase-negative species from the newly described fifth group got included in the *M. smegmatis* group.

In the present study, as seen in Table 1, 13.63% isolates of *M. fortuitum* group and 7.14% isolates of *M. smegmatis* group were susceptible to amikacin. Intermediate sensitivity was seen to amikacin in 7.14% isolates of *M. smegmatis* group. All isolates of *M. chelonae–abscessus* group were resistant to amikacin. A study from New South Wales showed high rates of resistance to amikacin (68%) in *M. chelonae–abscessus* group.[5] However, sensitivity to amikacin was 100% for *M. fortuitum* group in studies from Taiwan and Korea and it ranged from 94 to 100% for *M. chelonae–abscessus* group.[4,6] In our study, resistance to amikacin was high, may be because our patients had been hospitalized for long periods and had received prior aminoglycoside therapy. Resistance to amikacin may be due to indiscriminate aminoglycoside therapy used as a single drug. Resistance of *M. fortuitum* group following previous aminoglycoside therapy has been described.[7]

Macrolides and clarithromycin are important agents for treatment of pulmonary and cutaneous infections caused by *M. chelonae*, *M. abscessus*, and majority of *M. fortuitum*. In our study, all the isolates of RGM were resistant to clarithromycin. A study from New South Wales also showed 70% of *M. fortuitum*

Table 1 – Antimicrobial susceptibility of rapidly growing mycobacteria by broth microdilution.

Antimicrobial agents	No. of isolates of *M. fortuitum* group (*n* = 22)			No. of isolates of *M. smegmatis* group (*n* = 14)			No. of isolates of *M. chelonae–abscessus* group (*n* = 4)		
	S	I	R	S	I	R	S	I	R
Amikacin	3 (13.63%)	–	19 (86.36%)	1 (7.14%)	1 (7.14%)	12 (85.71%)	–	–	4 (100%)
Cefoxitin	4 (18.18%)	1 (4.54%)	17 (77.27%)	–	1 (7.14%)	13 (92.85%)	–	–	4 (100%)
Ceftriaxone	5 (22.72%)	–	17 (77.27%)	–	1 (7.14%)	13 (92.85%)	–	–	4 (100%)
Ciprofloxacin	–	–	22 (100%)	–	–	14 (100%)	–	–	4 (100%)
Clarithromycin	–	–	22 (100%)	–	–	14 (100%)	–	–	4 (100%)
Minocycline	–	–	22 (100%)	–	–	14 (100%)	–	–	4 (100%)
Imipenem	7 (31.81%)	–	15 (68.18%)	–	–	14 (100%)	–	–	4 (100%)
Linezolid	–	–	22 (100%)	–	–	14 (100%)	–	–	4 (100%)
Tobramycin	–	–	22 (100%)	–	–	14 (100%)	–	–	4 (100%)
Gatifloxacin	–	4 (18.18%)	18 (81.81%)	–	–	14 (100%)	–	1 (25%)	3 (75%)
Amoxicillin–clavulanic acid	1 (4.54%)	6 (27.27%)	15 (68.18%)	–	2 (14.28%)	12 (85.71%)	–	2 (50%)	2 (50%)
Trimethoprim–sulfamethoxazole	7 (31.81%)	–	15 (68.18%)	2 (14.28%)	–	12 (85.71%)	–	–	4 (100%)

S, susceptible; I, intermediate susceptible; R, resistant.

to be resistant to clarithromycin.[5] Authors from Taiwan showed 20% of *M. fortuitum* group, 49% of *M. chelonae*, and 11% of *M. abscessus* isolates to be resistant to clarithromycin.[4] Intrinsic macrolide resistance in *M. smegmatis* is conferred by a novel erm gene, erm(38), which is inducible and shows cross-resistance to lincosamides but not to streptogramin B.[8] A similar phenotype is found with macrolide-resistant *M. fortuitum*. In *M. chelonae*, resistance develops following monotherapy and is conferred by mutation in the 23S rRNA gene.[9]

Also, *M. fortuitum* group was not speciated further and many of the isolates may have been the third biovariant sorbitol-positive group, which is known to be clarithromycin resistant. Also, 35% of the RGM isolates in our study belonged to the *M. smegmatis* group, which is usually resistant to macrolides.

Among the quinolones, all our isolates of RGM were resistant to ciprofloxacin. Eighteen (81.81%) *M. fortuitum* group isolates, three isolates (75%) belonging to *M. chelonae–abscessus*, and all 14 isolates of *M. smegmatis* group were resistant to gatifloxacin. Our results conformed with those from Taiwan, where gatifloxacin resistance was seen in 20% of *M. fortuitum group*, 56% of *M.* chelonae, and 76% of *M. abscessus* isolates. The same study showed 33% of *M. fortuitum*, 97% of *M. chelonae*, and 95% of *M. abscessus* isolated to be resistant to ciprofloxacin.[4] Resistance data are known to vary geographically. Acquired mutational resistance to the newer quinolones limits the use of this class of drugs as monotherapy.[10]

In our study, four isolates (18.18%) of *M. fortuitum* group were found to be sensitive to cefoxitin and one each of *M. fortuitum* group (4.54%) and *M. smegmatis group* (7.14%) showed intermediate sensitivity. Our findings correlated with that obtained from Taiwan, where sensitivity of *M. fortuitum* to cefoxitin was 19%.[4] In the present study, ceftriaxone inhibited five isolates of *M. fortuitum* group (22.72%) and was intermediately active against one isolate of *M. smegmatis* (7.14%). All isolates of *M. chelonae–abscessus* group in our study were resistant to cefoxitin and ceftriaxone. *M. chelonae* is known to be uniformly resistant to cefoxitin. High degrees of resistance to cefoxitin were also seen in *M. chelonae* and *M. abscessus* in a study from Taiwan, where sensitivity was found to be 5% and 3%, respectively.[4]

Imipenem was active against seven (31.81%) of *M. fortuitum* group isolates in the present study. The sensitivity to imipenem among *M. fortuitum* was 61% in Taiwan and 98% in Korea.[4,6] Thus, resistance of *M. fortuitum* group to imipenem was more in our study. None of the isolates in *M. chelonae–abscessus* group in our study were sensitive to imipenem. High degrees of resistance to imipenem have been seen in Korea, where only 8% of *M. abscessus* were sensitive.[6] MICs for imipenem are problematic with isolates of *M. abscessus* and *M. chelonae* due to their lack of reproducibility. Imipenem may still be useful clinically in treatment regimens for these organisms.[11]

In our study, in the *M. fortuitum* group, only one isolate (4.54%) was sensitive while six (27.27%) showed intermediate sensitivity to amoxicillin–clavulanic acid. Two isolates each of *M. smegmatis* group (14.28%) and *M. chelonae–abscessus* group (50%) also showed intermediate sensitivity.

None of the RGM isolates in the present study were sensitive to minocycline. Minocycline resistance in our study correlated with doxycycline resistance for *M. chelonae–abscessus* group in the Taiwan study.[4]

All RGM isolates in our study were resistant to linezolid by broth microdilution. In the Taiwan study, 25% of *M. fortuitum*, 5% of *M. chelonae*, and 42% of *M. abscessus* were resistant to linezolid.[4]

In our study, seven isolates of *M. fortuitum* group (31.81%) and two (14.28%) of *M. smegmatis* group were sensitive to trimethoprim–sulfamethoxazole by broth microdilution. None of the *M. chelonae* isolates, only 1% of *M. abscessus*, and 49% of *M. fortuitum* were sensitive to cotrimoxazole in Taiwan, which is similar to our study.[4]

High degree of resistance seen in RGM in our study is alarming. Broth microdilution should include drugs like moxifloxacin, meropenem, ertapenem, and aminoglycosides, e.g. kanamycin. However, breakpoints and interpretive values for these drugs have to be established.

In conclusion, variable sensitivity to different antimicrobials exists in all groups; hence, performing antimicrobial susceptibility test is important before initiating therapy.

Accurate species identification could guide empiric antibiotic therapy. Communication between the clinician and laboratorian is essential for determining the importance and extent of the identification for a rapidly growing mycobacterial isolate.

Author contributions

All authors contributed substantially to the study. Specifically, Reena Set conceptualized, designed, obtained funding for, and monitored the study; Geeta Gole conducted all speciation and microbroth dilution tests, including reading and reporting of results, overall data management, and contributed to data analysis and interpretation of data; Nishat Khan helped in drafting the article and revising it critically for important intellectual content, and Jayanthi Shastri revised it critically and gave the final approval of the version to be published.

Conflicts of interest

The authors have none to declare.

Acknowledgment

We are grateful to B.Y.L. Nair Hospital Research Society for funding this project.

REFERENCES

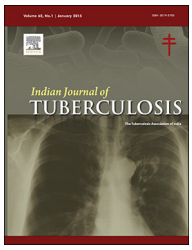
1. Shenai S, Rodrigues C, Mehta A. Time to identify and define nontuberculous mycobacteria in a tuberculosis-endemic region. *Int J Tuberc Lung Dis*. 2010;14:1001–1008.
2. Winn Jr WC, Allen SD, Janda WM, et al. *Koneman's Colour Atlas and Textbook of Diagnostic Microbiology*. 6th ed.

Philadelphia: Lippincott Williams and Wilkins; 2006: 1065–1124.
3. Woods GL, Brown Elliot BA, Desmond EP, et al. *Susceptibility Testing of Mycobacteria, Nocardia and Other Aerobic Actinomycetes; Approved Standard M24-A*. Pennsylvania: CLSI, Wayne; 2003:40.
4. Yang SC, Hsueh PR, Lai HC, et al. High prevalence of antimicrobial resistance in rapidly growing mycobacteria in Taiwan. *Antimicrob Agents Chemother*. 2003;47:1958–1962.
5. Foo H, Van Hal S, Jelfs P, Gilbert GL. Antimicrobial resistance in nontuberculous mycobacteria in New South Wales 2002–2008. *Int J Antimicrob Agents*. 2009;34:182–184.
6. Lee SM, Kim JM, Jeong J, et al. Evaluation of the broth microdilution using 2,3-diphenyl-5-thiethyl-(2)-tetrazolium chloride for rapidly growing mycobacteria susceptibility testing. *J Korean Med Sci*. 2007;22:784–790.
7. Plemmons RM, McAllister CK, Liening DA, Garces MC. Otitis media and mastoiditis due to *M. fortuitum*: case report, review of four cases, and a cautionary note. *Clin Infect Dis*. 1996;22:1105–1106.
8. Nash KA. Intrinsic macrolide resistance in *Mycobacterium smegmatis* is conferred by a novel erm Gene, erm(38). *Antimicrob Agents Chemother*. 2003;47:3053–3060.
9. Tebas P, Sultan F, Wallace Jr RJ, Fraser V. Rapid development of resistance to clarithromycin following monotherapy for disseminated *Mycobacterium chelonae* infection in a heart transplant patient. *Clin Infect Dis*. 1995;20:443–444.
10. Brown-Elliott BA, Wallace Jr RJ, Crist CJ, Mann L, Wilson RW. Comparison of in vitro activities of gatifloxacin and ciprofloxacin against four taxa of rapidly growing mycobacteria. *Antimicrob Agents Chemother*. 2002;46: 3283–3285.
11. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175:367–416.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Original Article

Non-communicable disease comorbidities and risk factors among tuberculosis patients, Meghalaya, India

Bibha Marak [a], *Prabhdeep Kaur* [b,*], *Sudha R. Rao* [b], *Sriram Selvaraju* [c]

[a] *Department of Health and Family Welfare, Government of Meghalaya, East Garo Hills, Meghalaya, India*
[b] *National Institute of Epidemiology (Indian Council of Medical Research), Tamil Nadu Housing Board, Chennai, India*
[c] *National Institute for Research in Tuberculosis, Chennai, India*

ARTICLE INFO

Article history:
Received 19 February 2015
Accepted 21 July 2015
Available online 4 June 2016

Keywords:
Tuberculosis
India
Diabetes
Hypertension
Tobacco

ABSTRACT

We did cross-sectional study to estimate the prevalence of tobacco, alcohol use, hypertension and diabetes among tuberculosis (TB) patients in comparison to the non-TB patients in East Garo Hills District, Meghalaya, India. We surveyed 110 TB patients attending outpatient TB clinic and 110 age/sex matched non-TB subjects from the general outpatient department as comparison group. Prevalence of ever smoking was 74.5% and 55.4%; alcohol consumption 31.0% and 22.3%; hypertension 24.5% and 17.3%; diabetes 7.5%, 4.5% among TB patients and non-TB subjects, respectively. NCD and TB programmes need integration in the primary care for screening, counselling and treatment of NCD comorbidities.

1. Introduction

Tuberculosis (TB) is a major health problem in Meghalaya state, the prevalence being 593/100,000 population.[1] Tobacco smoking and alcohol consumption were the risk factors associated with pulmonary TB in various studies from India.[2,3] India has rising burden of non-communicable diseases (NCDs), with hypertension and diabetes being two highly prevalent NCDs.[4,5] There are no data on the prevalence of risk behaviours and NCD comorbidities among TB patients in the tribal populations of the northeastern region of India. Therefore, we conducted a cross-sectional study to estimate the prevalence of behavioural risk factors tobacco and alcohol consumption and comorbidities hypertension and diabetes among tribal TB patients in comparison to non-TB patients in East Garo Hills district, Meghalaya, India.

2. Methods

The study population consisted of line list of TB patients registered under RNTCP programme between July 2013 and April 2014, aged 18 years and above, on treatment in public sector health facilities in the East Garo Hills district, Meghalaya, India. We selected age- (±5 year age groups) and

* *Corresponding author at*: National Institute of Epidemiology (Indian Council of Medical Research), # R-127, 3rd Avenue, Tamil Nadu Housing Board, Chennai 600 077, India. Tel.: +91 4426136233; fax: +91 4426136233.
E-mail address: kprabhdeep@gmail.com (P. Kaur).

http://dx.doi.org/10.1016/j.ijtb.2015.07.018

sex-matched subjects visiting the outpatient department of the same health facility for minor ailments as the comparison group. The sample size was 68 for each group, with a total sample size of 136 for the two groups assuming 80% prevalence of tobacco smoking among the TB patients and 55% prevalence in the general population.[2] Other assumptions were 95% confidence level, 80% power and 10% non-response. The study was approved by the Institutional Ethics Committee.

2.1. Data collection

Demographic and behavioural risk factors were collected using semi-structured questionnaire in the local language. We collected data regarding socio-economic status, use of tobacco/alcohol and use of biomass fuel. Blood pressure was measured twice using sphygmomanometer and average of the two readings was taken. Random capillary glucose (RCG) and fasting capillary glucose (FCG) after 10 h fasting were taken using Accuchek Glucometer.

2.2. Operational definitions

TB case: A patient in whom tuberculosis has been confirmed by bacteriology or diagnosed by a clinician as per RNTCP criteria.[6]

Current smoker: A person who smoked at the time of the survey either daily or occasionally.

Current alcohol consumer: Those who have consumed one or more than one drink of alcohol in the year preceding the survey.

Hypertension: A respondent with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or history of previously known disease as per WHO criteria.[7]

Diabetes: Diagnosed by FCG of ≥126 mg/dl or RCG of ≥200 mg/dl with symptoms or history of previously known disease.[8]

2.3. Statistical analysis

We compared the prevalence of various risk factors/comorbidities in the TB and non-TB subjects by χ^2 test. All analyses were two-tailed and p-value <0.05 was considered statistically significant. Epi-info version 3.5.3 was used for the analysis.

3. Results

We surveyed 110 TB patients and the response rate was 92.0% among the line-listed patients. We surveyed 110 subjects in the comparison group. One-third of the subjects were 18–24 years of age and 63% were males in both the groups (Table 1). There was no statistically significant difference in majority of the socio-demographic characteristics in both the groups.

Prevalence of current smoking was higher in non-TB as compared to TB patients and vice versa for the past smokers ($p < 0.01$). Current alcohol use was higher in TB patients (35.5% vs. 29.1%). Prevalence of hypertension among TB subjects was higher as compared to non-TB subjects (24.5% vs. 17.3%). Prevalence of newly detected diabetes among TB population was 7.3% as compared to 4.5% in the comparison group and the difference was not statistically significant (Table 2). Median fruit and vegetable intake was three servings a day in both the groups.

Table 1 – Distribution of socio-demographic characteristics of the tuberculosis patients and non-TB study population in East Garo Hills District, Meghalaya, 2014 (N = 220).

Variables	TB (N = 110)		Non-TB (N = 110)		p-value
	n	%	n	%	
Age (in years)					
18–24	36	32.7	30	27.3	0.663
25–34	22	20.0	28	25.5	
35–44	19	17.3	20	18.2	
45–54	21	19.1	16	14.5	
≥55	12	10.9	16	14.5	
Sex					
Male	70	63.6	70	63.6	0.889
Female	40	36.4	40	36.4	
Marital status					
Married	55	50.0	80	72.7	<0.01
Others	55	50.0	30	27.3	
Occupation					
Agriculturist	30	27.3	37	33.6	0.289
Manual labour	12	10.9	19	17.3	
Services	14	12.7	15	13.6	
Homemaker	25	22.7	20	18.2	
Others	29	26.4	19	17.3	
Type of house					
Kutcha	78	65.0	68	61.8	0.157
Semi-pucca	34	28.3	24	21.8	
Pucca	8	6.7	18	16.4	
Education					
Illiterate	16	14.5	22	20.0	0.092
1–5 years of schooling	21	19.1	27	24.5	
6–8 years of schooling	18	16.4	17	15.5	
9 years of schooling and above	55	50.0	44	40.0	

4. Discussion

Our study results indicated high prevalence of tobacco and alcohol consumption not only among the TB patients but also among the non-TB subjects in Garo tribal population of East Garo Hills. This might be due to the culturally acceptable practice of alcohol consumption and traditional practice of using leaf rolled tobacco for smoking. We need locally and culturally relevant intervention strategies for tribal populations to modify these behaviours. These risk factors not only increase the NCD burden but also increase the incidence of TB as observed in another study in the Saharia tribal group in Madhya Pradesh where smoking (OR 1.8) and alcohol (OR 1.7) were the risk factors for TB.[3] A pilot study on integrating 'brief advice' in TB control programme to promote tobacco cessation in Vadodara, Gujarat showed that 67% quit rate of tobacco at the end of treatment.[9] This can be one of the interventions that can be scaled up in TB control programme to improve the treatment outcome and decrease mortality from TB in settings where smoking rates are high.

Table 2 – Prevalence of behavioural risk factors, hypertension and diabetes among tuberculosis patients and non-TB study population in East Garo Hills District, Meghalaya, 2014 (N = 220).

Variables	TB		Non-TB		p-value
	n = 110	%	n = 110	%	
Tobacco use					
Current smoker	37	33.6	42	38.2	<0.01
Past-smoker	45	40.9	19	17.3	
Non-smoker	28	25.5	49	44.5	
Smokeless tobacco use					
Current use	68	61.8	74	67.3	0.443
Past use	11	10.0	8	7.3	
Never use	31	28.2	28	25.5	
Alcohol consumption					
Present consumer	39	35.5	32	29.1	0.046
Past consumer	29	26.4	17	15.5	
Never used	42	38.2	61	55.5	
Tobacco and alcohol					
Ever consumed both	64	58.2	36	32.7	<0.01
Wood use as cooking fuel					
Current use	99	90.0	97	88.2	0.866
Past use	7	6.4	12	10.9	
Never use	4	3.6	1	0.9	
Hypertension					
Hypertension self-reported	9	8.2	6	5.5	0.593
Hypertension newly detected	18	16.4	15	13.6	0.706
Overall hypertension	27	24.5	21	17.3	0.414
Diabetes					
Diabetes mellitus newly detected	8	7.3	5	4.5	0.567

Prevalence of self-reported hypertension was considerably low in our study. Therefore, high burden of undetected hypertension needs to be addressed with the appropriate screening and other intervention strategies. Prevalence of diabetes in our study was lower as compared to a large multicentric study by India Tuberculosis-Diabetes Study group among TB patients that reported 13% prevalence of the disease.[10] However, the study had many urban sites and did not include any site from the north eastern part of India. The study established the feasibility of diabetes screening among TB patients in the programme setting. Recent policy decision to include diabetes screening in the TB programme will be an important initiative to improve comorbidity detection and management among TB patients. One of the limitations of our study was that plasma glucose could not be estimated due to lack of auto analyser facility.

TB patients as well as non-TB patients in the tribal East Garo Hills district had high burden of multiple risk factors and comorbidities. The programmes that address the NCD and TB need to be integrated at the primary care level for screening, counselling and treatment. Capacity building of the human resources for counselling and management, development of infrastructure and availability of drugs for NCDs at primary care level will be needed to improve the patient outcomes.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. International Institute for population Sciences. *National Family Health Survey-3, 2005–2006*. Mumbai: International Institute for population Sciences; 2007.
2. Gajalakshmi V, Peto R. Smoking, drinking and incident tuberculosis in rural India: population-based case–control study. *Int J Epidemiol*. 2009;38(4):1018–1025.
3. Rao VG, Gopi P, Bhat J, Yadav R, Selvakumar N, Wares DF. Selected risk factors associated with pulmonary tuberculosis among Saharia tribe of Madhya Pradesh, central India. *Eur J Public Health*. 2012;22(2):271–273.
4. Anchala R, Kannuri NK, Pant H, et al. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J Hypertens*. 2014;32 (6):1170.
5. Anjana R, Pradeepa R, Deepa M, et al. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. *Diabetologia*. 2011;54 (12):3022–3027.
6. World Health Organization. *TB Case Definitions; TB Diagnostics and Laboratory Strenghtening and TB Monitoring and Evaluation, Stop TB Department* 2011. Available from: *http://www.who.int/tb/publications/global_report/2008/table_a2_1/en/* [accessed 23.06.14].
7. Whitworth J. 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003;21(11):1983.
8. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2005;28:S37.
9. Kaur J, Sachdeva KS, Modi B, et al. Promoting tobacco cessation by integrating 'brief advice' in tuberculosis control programme. *WHO South-East Asia J Public Health*. 2013;2(1):28.
10. Kumar A, Jain D, Gupta D, Satyanarayana S, Zachariah R, Harries A. Screening of patients with tuberculosis for diabetes mellitus in India. *Trop Med Int Health*. 2013;18 (5):636–645.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Case Report

Multiple lumps in the breast due to *Mycobacterium fortuitum*

Shirish S. Chandanwale [a,*], *Ishita Gulati* [b], *Dadaso S. Baravkar* [c], *Sumedha P. Shinde* [c], *Neha Mishra* [c]

[a] *Professor, Department of Pathology, Dr D Y Patil Medical College, Pimpri, Pune 411018, India*
[b] *Junior Resident, Department of Pathology, Dr D Y Patil Medical College, Pimpri, Pune 411018, India*
[c] *Senior Resident, Department of Pathology, Dr D Y Patil Medical College, Pimpri, Pune 411018, India*

ARTICLE INFO

Article history:
Received 9 May 2015
Accepted 13 July 2015
Available online 15 March 2016

Keywords:
Tuberculosis
NTM
Fortuitum
Mycobacterium
Breast

ABSTRACT

Although breast tissue is the most resistant to tuberculosis, its incidence is increasing worldwide. High incidence of breast tuberculosis is presumed in India. The rapidly growing nontubercular mycobacteria, such as *Mycobacterium fortuitum* and *Mycobacterium chelonae*, are of increasing clinical importance because infections due to these organisms are often hospital acquired. The true incidence of *M. fortuitum* is unknown but it has been estimated to be between 4 and 6 cases per one million people. It causes skin or soft tissue infections following trauma or surgery. Breast infection with *M. fortuitum* is very uncommon. The most common clinical presentation of breast tuberculosis is a painless lump. Multiple lumps are rarely reported. The culture and molecular studies are the keystone for differentiation of various mycobacterium species. We report one such case of a 25-year-old female presenting with multiple painless lumps due to *M. fortuitum* infection in the left breast.

1. Introduction

Tuberculosis (Tb) remains one of the leading cause of death from infectious diseases worldwide. One-third of all new cases are in India and China.[1] Breast is one of the least common locations for tuberculosis infection with reported incidence of 0.3–5% in endemic regions.[2,3] Breast lesions caused by nontubercular mycobacteria (NTM) have been recently reported. The rapidly growing NTM, *Mycobacterium fortuitum* and *Mycobacterium chelonae*, are of increasing clinical importance because, infections due to these organisms are often hospital acquired and there is emerging importance in both sporadic infections and outbreak settings. Breast infection with NTM fortuitum is very uncommon. Few reports are published in the past. Majority reports are following breast implant and reconstructive surgery. Most common clinical presentation of breast tuberculosis is a painless lump with or without discharging sinuses.[4–6] Multiple lumps are rarely reported.[2,3] We report one such case of multiple lumps in the left breast due to NTM fortuitum in a 25-year-old female with a history of minor surgery.

* *Corresponding author at*: 75/1+2/1 Krishna Apartments, New Sangvi, Pune 411027, Maharashtra, India. Tel.: +91 9890144517; fax: +91 020 27420605.
E-mail address: shirishchandanwale@gmail.com (S.S. Chandanwale).
http://dx.doi.org/10.1016/j.ijtb.2015.07.016

2. Case report

A 25-year-old female presented with complaint of multiple painless lumps in the left breast, gradually increasing in size since 3 months. There was no history of fever. She had two children; the youngest was 9-month-old to whom she breast-feed until 7 months. She gave history of some minor operative procedure in the same breast 2 months back in a private hospital. Pathology reports suggested that it was a galactocele.

On physical examination, four, firm, painless lumps [2.3 cm × 1.1 cm, 2.0 cm × 1.4 cm, 1.5 cm × 1.4 cm and 1.5 cm × 0.6 cm each] were palpable in the left breast, lower inner quadrant. Overlying skin was normal. A scar measuring 1.5 cm × 0.6 cm was visible in the same breast (Fig. 1a). A lymph node measuring 1.4 cm × 1.0 cm was palpable in the left axilla. Right breast was normal. Ultrasonography of the left breast revealed multiple hypoechoic lesions with vascularity (Fig. 1b). A diagnosis of adenosis with degenerative changes was suggested. Patient was seronegative for human immunodeficiency virus (HIV).

Fine needle aspiration (FNA) was done from all the swellings and aspirated yellowish white pus like material. Smears were stained with Leishmann and Ziehl–Nielsen (ZN) stains.

Microscopy showed a background of necrotic debris and viable neutrophils. Many scattered epithelioid cells were seen (Fig. 2a). Few histiocytic giant cells and clusters of cohesive ductal epithelial cells were seen (Fig. 2b). Ziehl–Nielsen (ZN) stain showed many acid fast bacilli (AFB) (Fig. 2c). A diagnosis of breast tuberculosis was made. Aspiration from the left axillary lymph node revealed reactive lymphadenopathy. Subsequent radiological examination revealed no significant findings in the lungs or pleura. Tuberculin test was strongly positive. Patient was started on standard antitubercular treatment for six months (Category I) as per Revised National Tuberculosis Control Programme (RNTCP). After 1 month, there was little improvement clinically. Aspiration was done again and pus was sent for AFB culture. Lowenstein–Jensen culture report was NTM (Rapid growers) growth. The INNO-LiPA Mycobacteria (LiPA) assay identified the species as *M. fortuitum*.

3. Discussion

Tb is one of the leading causes of morbidity and mortality in developing and developed countries. Although breast tissue is most resistant to Tb, incidence is increasing worldwide due to increase in number of geriatric population, emergence of drug resistant strains and HIV infection.[2,3] High incidence of breast TB is presumed in India. It is often misdiagnosed as pyogenic abscess or carcinoma in breast.[7] Breast infection due to NTM is very uncommon. Breast infection with *M. fortuitum* is very uncommon. Mammography or ultrasonography is unreliable in distinguishing it from pyogenic abscess and carcinoma, if well-defined features are absent.[8]

Primary infection of the breast can occur, though most frequently it is secondary to a tuberculous focus in the lungs, pleura or lymph nodes, which may not be detected on radiological examination or clinically.[9] *Mycobacterium fortuitum* has been isolated from water, soil and dust and usually causes skin or soft tissue infections following trauma or surgery. It has been found to be resistant to several types of disinfectants.

Breast TB usually affects young, multiparous and lactating women. It can occur in males. Clinical manifestations of breast TB are highly variable. Constitutional symptoms like fever, weight loss, anorexia and night sweats are often absent. Similar observations were made in our case.[2] Upper and outer quadrant of the breast is more commonly involved owing to the proximity to axillary lymph nodes. Multiple lumps in

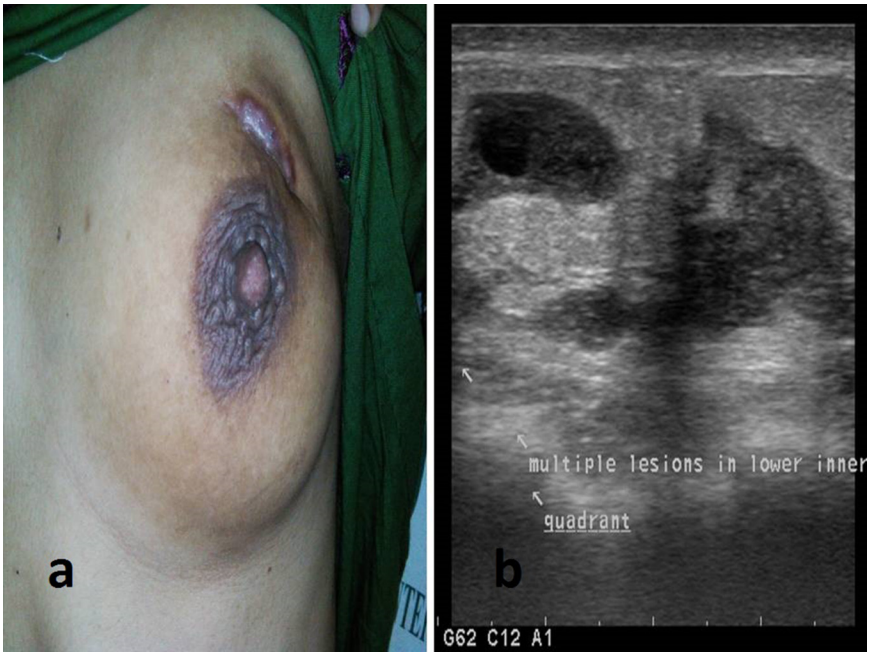


Fig. 1 – (a) Multiple lumps and scar of previous surgery. (b) Multiple hypoechoic lesions on ultrasonography.

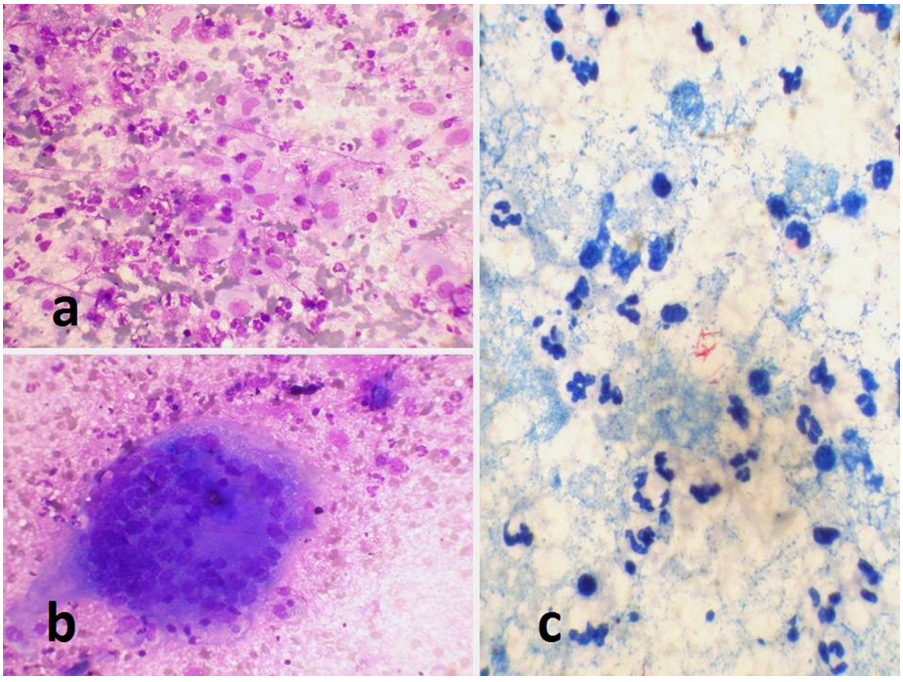


Fig. 2 – (a) FNA smears showed necrotic debris, viable polymorphs and scattered epithelioid cells (Leishmann ×400). (b) Histiocytic giant cells (Leishmann stain ×400). (c) Acid fast bacilli (Ziehl–Nielsen ×1000).

breast are less common and rarely reported.[2,3] In our case, four, firm, painless lumps were palpable in the lower and inner quadrant.

Fine needle aspiration continues to remain an important diagnostic tool for breast tuberculosis. Epithelioid granulomas with caseous necrosis are a reliable finding on FNA for definitive diagnosis of breast tuberculosis. In the absence of caseous necrosis, demonstration of AFB on FNA smears or in culture examination or PCR can establish definitive diagnosis. Occasionally, FNA smears are dominated by necrotic debris and neutrophils. In such cases, careful search of epithelioid cells and demonstration of AFB in cytology smears or by culture examination can establish definitive diagnosis of breast tuberculosis,[9] as seen in our case.

Cases in which patients are not responsive to standard antitubercular regimen, the culture and molecular studies are the keystone for differentiation of mycobacterium species. In general LiPA is a reliable genetic test for differentiation of various mycobacterium species.[10]

Patient was started on a daily regimen of rifampicin (450 mg), isoniazid (300 mg), ethambutol (800 mg), pyrazinamide (1250 mg) once a day and clarithromycin (500 mg) twice a day. Patient was on close follow-up, and after 1 month, patient showed improvement clinically.

4. Conclusion

Although breast tissue is most resistant to tuberculosis infection, incidence of breast TB is increasing worldwide and presumed to be higher in an endemic country like India. The rapidly growing NTM, *M. fortuitum* and *M. chelonae*, are of increasing clinical importance. When any multiparous woman is presenting with painless multiple breast lumps, tuberculosis should be kept in mind. If the breast FNA smears are dominated by suppurative inflammatory infiltrate, scattered epithelioid cells on the background and AFB, a definitive diagnosis of tuberculosis is established. The culture and molecular studies are the keystone for differentiation of various mycobacterium species. In general, LiPA is a reliable genetic test for differentiation of various mycobacterium species.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Tuberculosis. *Bull WHO*. 1998;76(suppl 2):141–143.
2. Kao PT, Tu MY, Tang SH, Ma HK. Tuberculosis of the breast with erythema nodosum: a case report. *J Med Case Reports*. 2010;4:124.
3. Murat K, Mehmet T, Sule B, et al. Tuberculosis of breast. *Eur J Gen Med*. 2010;7:216–219.
4. Rimmer J, Hamilton S, Gault D. Recurrent mycobacterial breast abscesses complicating reconstruction. *Br J Plast Surg*. 2004;57:676–678.
5. Haiavy J, Topin H. *Mycobacterium fortuitum* infection in prosthetic breast implants. *Plast Reconstr Surg*. 2002;109:2124–2128.

6. Boettcher AK, Bengtson BP, Farber ST, Ford RD. Breast infections with atypical mycobacteria following reduction mammaplasty. *Aesthet Surg J*. 2010;30:542–548.
7. Kakkar S, Kapila K, Singh MK, Verma K. Tuberculosis of the breast. A cytomorphologic study. *Acta Cytol*. 2000;44:292–296.
8. Madhusudhan KS, Gamanagatti S. *Singapore Med J*. 2008;49 (1):e3–e5.
9. Tewari M, Shukla HS. Breast tuberculosis: diagnosis, clinical features and management. *Indian J Med Res*. 2005;122:103–110.
10. Suffys PN, da Silva Rocha A, de Oliveira M, et al. Rapid identification of Mycobacteria to the species level using INNO-LiPA Mycobacteria, a reverse hybridization assay. *J Clin Microbiol*. 2001;39:4477–4482.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Case Report

An outbreak of multidrug-resistant tuberculosis among a family

Sinem Iliaz [a,*], *Emel Caglar* [a], *Orhan Kaya Koksalan* [b], *Efsun Gonca Ugur Chousein* [a]

[a] *Yedikule Training and Research Hospital for Chest Disease and Thoracic Surgery, Department of Pulmonary Medicine, Zeytinburnu, Istanbul, Turkey*

[b] *Istanbul University, Institute for Medical Experimental Research, Molecular Tuberculosis Epidemiology Laboratory, Fatih, Istanbul, Turkey*

ARTICLE INFO

Article history:
Received 25 March 2015
Accepted 13 July 2015
Available online 4 June 2016

Keywords:
Multidrug resistance
Tuberculosis
Transmission
Contact

ABSTRACT

Tuberculosis is a major public health problem and it may be complicated by multidrug-resistant tuberculosis (MDR-TB). Wide transmission among immunocompetent contacts of the index case is possible. If you detect tuberculosis in two contacts of the index case, it is called an outbreak. The aim of our paper is to evaluate the characteristics of a MDR-TB outbreak affecting 7 people in a family treated during 2012–2014 in Istanbul Yedikule Training and Research Hospital for Chest Disease and Thoracic Surgery, Turkey. The cultures, spoligotyping, and DNA fingerprinting revealed the same *Mycobacterium tuberculosis* species as T1 genotype and ST53 subtype. All patients were negative for human immunodeficiency virus and free of other underlying diseases.

1. Introduction

Tuberculosis is a major public health problem. However, the treatment is harder if it is complicated by multidrug-resistant tuberculosis (MDR-TB). MDR-TB treatment is more complex and longer. Luckily, sustained epidemic spread of drug-resistant TB was considered unlikely.[1] Dye et al. showed that the prevalence of MDR-TB remained at low levels in majority of the world. Some parts of the world like the Baltic states, parts of India, Russia, and China have higher rates of MDR-TB.[1] Gandhi et al. reported a large cluster of extensive drug-resistant TB (XDR-TB) among HIV co-infected patients in a rural area of South Africa. In this study, genotyping of isolates revealed that 39 of 46 patients with XDR-TB were infected with similar strains.[2] There was another example of resistant TB outbreak among HIV-infected patients in New York in early 1990s.[3] These data provided an example that some drug-resistant strains may cause outbreaks among immunocompromised patients. Wide transmission among immunocompetent contacts of the index case is also possible. If you detect tuberculosis in

* *Corresponding author at*: Yedikule Training and Research Hospital for Chest Disease and Thoracic Surgery, Department of Pulmonary Medicine, Kazlicesme mah., Belgrat Kapi Yolu, No: 1, Posta kodu: 34020, Zeytinburnu, Istanbul, Turkey. Tel.: +90 212 664 17 00x1214; fax: +90 212 664 10 10.
E-mail address: snmkaraosman@gmail.com (S. Iliaz).

http://dx.doi.org/10.1016/j.ijtb.2015.07.009

two contacts of the index case, it is called an outbreak. The aim of our paper is to evaluate the characteristics of a MDR-TB outbreak within a family treated during 2012–2014 in Istanbul Yedikule Training and Research Hospital for Chest Disease and Thoracic Surgery, Turkey.

2. Cases

Our index case was a 19-year-old male (Case 1). He was diagnosed with smear positive pulmonary tuberculosis and had antituberculosis treatment with four major drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). In the fourth month of the treatment, smear positivity persisted and there was radiological progression in the chest X-ray. Drug susceptibility testing (DST) revealed MDR-TB with resistance for isoniazid, rifampicin, ethambutol, streptomycin, and ethionamide. According to these results, we started treatment for MDR-TB consisting of amikacin 1× 1 g intramuscular, ofloxacin 2× 400 mg tablets, cycloserine 3× 250 mg capsule, para-aminosalicylic acid 1× 12 g tablets, and pyrazinamide 1× 2000 g tablets. MDR-TB treatment continued for 24 months and the patient was cured finally.

Six other people consisting of the sister and the brother of index case, and four cousins living at a nearby house were diagnosed with tuberculosis within 12 months following diagnosis of the index case (Table 1). In a total of seven patients, four were male and three were female. The age of the patients ranged from 15 to 22 years. Except one of the patients (Case 2), all had positive sputum smears for acid-fast bacilli (ARB) and infiltration on chest X-ray. Case 2 was 17-year-old male. He had pleural effusion and no parenchymal lesion on chest X-ray. His sputum and pleural effusion were negative for ARB. Analysis of pleural effusion revealed exudative effusion with lymphocyte predominance and the biopsy of parietal pleura resulted in necrotizing granulomatous inflammation. The patient was diagnosed with tuberculous pleurisy and he took the firstline-antituberculosis treatment for 6 months. After 6 months, his chest X-ray revealed complete regression. Twenty months after the treatment, he was admitted to a hospital with seizure. After surgical brain biopsy, the cause of the seizure was defined as tuberculous granuloma of the brain. He was diagnosed with MDR-TB encephalitis and we started on anti-MDR-TB treatment based on the DST results of the index case. In all patients, MDR-TB treatment was started because of unresponsiveness to the firstline anti-TB treatment (progression in infiltration, persistent smear positivity).

All patients except for Case 2 with pleural tuberculosis had positive sputum smears prior to the anti-TB treatment. The cultures, spoligotyping, and DNA fingerprinting revealed the same *Mycobacterium tuberculosis* species as T1 genotype and ST53 subtype for four patients (Table 1). The DST revealed the same resistance pattern for all six smear positive patients. All patients were negative for human immunodeficiency virus (HIV) and free of other underlying diseases.

3. Discussion

Although tuberculosis is a common public health problem, MDR-TB is also becoming more important. Because treatment of resistant tuberculosis is very difficult and longer, careful contact screening and early diagnosis are very important in order to prevent disease spread. In the present study, we describe a MDR-TB outbreak among a family living at two nearby houses. It affected seven people in the same family. All patients were HIV-seronegative.

In order to maintain MDR-TB control, we must find new MDR-TB patients immediately and treat them. So, the contact screening program is so vital. The reason for widespread MDR-TB transmission in the community may be socially isolated overcrowded families similar to the family in our paper.[4–6] Our index case was living in a family with low socioeconomic status and with nine households living in the same house. Having primary MDR-TB in a country means your control program has some deficits and you did not detect the index case before widespread transmission of bacilli.

Our report revealed that six people were infected with the same *M. tuberculosis* strain and got MDR-TB (four cases have definite spoligotyping results and six patients had the same pattern in DST). Also, the case with pleural tuberculosis (Case 2) was probably infected by the same strain, but we could not isolate any microorganism. After the diagnosis of the index case with MDR-TB, the other family members with

Table 1 – Characteristics of the MDR-TB patients.

	Case 1 (Index)	Case 2 (cousin)	Case 3 (cousin)	Case 4 (sister)	Case 5 (cousin)	Case 6 (cousin)	Case 7 (brother)
Sex	Male	Male	Male	Female	Female	Female	Male
Age (years)	19	17	19	15	22	17	22
Spoligotyping results[a]	T1- ST53[b]		T1- ST53[b]	T1- ST53[b]			T1- ST53[b]
Site of TB	Lung	Pleurisy, encephalitis	Lung	Lung	Lung	Lung	Lung
WBC (cells/mm^3)	5800	8000	8200	6400	6960	5200	6780
ESR (mm/h)	66	57	93	80	42	19	14
CRP (g/dl)	71	77	156	69	58	13	27

TB: tuberculosis; WBC: white blood cells; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
[a] Spoligotyping was not performed in Cases 2, 5, and 6.
[b] T1 genotype ST53 subtype.

the diagnosis of tuberculosis might be started on anti-MDR-TB treatment directly. However, we switched to anti-MDR-TB treatment in a few months when our patients showed progression on chest X-ray or the smears remained positive. According to the World Health Organization (WHO), strengthening the laboratory network in conjunction with improvement of surveillance is imperative.[7] In the light of this information, DST is performed even for the first sputum sample of TB patients in our country.

In the study of Abakay et al., 34 MDR-TB patients were detected and only 14.5% of their contacts got active TB.[8] In our study, disease spread rate was markedly high. There were nine people living in the house of the index case and three (37.5%) of them got MDR-TB. In general, 5–10% of contacts develop active disease within 2 years of the primary infection.[9] Coinfection with HIV increases this risk considerably.[10] Although all patients presented in this study were negative for HIV, rate of progression to active TB disease was considerably high. All patients in our report were young adults and students. The index case helped the other six patients with their school study and homeworks for three times in a week for three to four hours at every session. This close contact may be related with high transmission rate of MDR-TB in our report.

In conclusion, in order to prevent spread of resistant TB, it is important to have early DST, starting on anti-MDR-TB treatment immediately, having directly observational treatment strategy (DOTS) and close follow-up of the contacts. We must take into consideration beginning directly with anti-MDR-TB treatment if close contacts of the index case are diagnosed with active TB.

Authorship

Emel Caglar critically revised the paper. Orhan Kaya Koksalan analyzed the sputum samples of the patients for *Mycobacterium tuberculosis* species determination. Efsun Gonca Ugur Chousein, Emel Caglar, and Sinem Iliaz followed up the patients. Sinem Iliaz wrote the paper.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? *Proc R Soc Lond B: Biol Sci.* 2001;268:45–52.
2. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet.* 2006;368:1575–1580.
3. Moss AR, Alland D, Telzak E, et al. A city-wide outbreak of a multiple-drug resistant strain of *Mycobacterium tuberculosis* in New York. *Int J Tuberc Lung Dis.* 1997;1:115–121.
4. Maguire H, Dale JW, McHugh TD, et al. Molecular epidemiology of tuberculosis in London 1995–7 showing low rate of active transmission. *Thorax.* 2002;57:617–622.
5. Lillebaek T, Andersen AB, Bauer J, et al. Risk of *Mycobacterium tuberculosis* transmission in a low-incidence country due to immigration from high-incidence areas. *J Clin Microbiol.* 2001;39:855–861.
6. Borgdorff MW, Nagelkerke N, van Soolingen D, de Haas PEW, Veen J, van Embden JD. Analysis of tuberculosis transmission between nationalities in the Netherlands in the period 1993–1995 using DNA fingerprinting. *Am J Epidemiol.* 1998;147:187–195.
7. Abdel Aziz M, Wright A. The World Health Organization/International Union Against Tuberculosis and Lung Disease global project on surveillance for anti-tuberculosis drug resistance: a model for other infectious diseases. *Clin Infect Dis.* 2005;41(suppl 4):S258–S262.
8. Abakay A, Tanrikulu AC, Abakay O, Senyigit A, Isik R. Factors that affect the transmission risk during contact with multidrug resistant tuberculosis. *J Clin Exp Invest.* 2010;1(1):31–36.
9. Zeidberg LD, Gass RS, Dillon A, Hutcheson RH. The Williamson County tuberculosis study. A twenty-four-year epidemiologic study. *Am Rev Respir Dis.* 1963;87:1–88.
10. Di Perri G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet.* 1989;2:1502–1504.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/

Case Report

"Cryptic" mediastinal tuberculosis with myasthenia-thymoma complex

George Jose Valooran [a], Shiv Kumar Nair [b,*], Krishnan Chandrasekharan [a], Sunitha Thomas [c], Joejo John [c]

[a] Consultant, Department of Cardiovascular and Thoracic Surgery, Rajagiri Hospital, Chunangamvely, Aluva, Kochi, Kerala 683112, India
[b] Senior Consultant and HOD, Department of Cardiovascular and Thoracic Surgery, Rajagiri Hospital, Chunangamvely, Aluva, Kochi, Kerala 683112, India
[c] Consultant, Department of Pathology, Rajagiri Hospital, Chunangamvely, Aluva, Kochi, Kerala 683112, India

ARTICLE INFO

Article history:
Received 23 July 2015
Accepted 6 January 2016
Available online 15 April 2016

Keywords:
Tuberculosis
Myasthenia gravis
Invasive thymoma
Maximal thymectomy
Anti-tubercular therapy

ABSTRACT

Mediastinal tuberculosis, although common in endemic areas, is rare in association with myasthenia-thymoma complex. Immunosuppressive therapy for myasthenia with thymoma might increase the susceptibility for mediastinal tuberculosis. Previous reports suggest aggravation of myasthenic symptoms with this association. This rare combination of pathologies adds to the diagnostic dilemma of the surgeon. Further research is warranted in the management aspects of this combination as regards to the timing of radiotherapy, weaning of immunosuppression and anti-tubercular therapy after maximal thymectomy. This case report emphasises the possibility of mediastinal tuberculosis as a differential diagnosis for mediastinal lymphadenopathy in the setting of a preoperative diagnosis of invasive thymoma.

1. Introduction

Thymoma is reported to be the commonest mediastinal mass by some authors excluding mediastinal lymph node enlargements.[1] The association of myasthenia gravis with thymoma is well documented with a 15% concurrence.[2] The presence of mediastinal lymph nodes in the setting of a thymic lesion tilts the diagnosis in favour of invasive thymoma with an incidence of up to 41%, especially, above the age of 40 years.[3] Primary mediastinal tubercular [MT] lymphadenitis, on the other hand, is relatively common in tuberculosis [TB] prevalent areas.[4] Here, we report the rare combination of an invasive thymoma, myasthenia gravis and MT in a middle-aged woman, probably a consequence of immunosuppressive therapy.

2. Case

A fifty-seven-year old woman, known diabetic, presented with drooping of both eyelids and excessive fatigue for the past 3 months. There was no history of any recent weight loss, evening pyrexia or contact with tubercular infection. On evaluation, she was found to be positive for anti-acetyl cholinesterase antibodies with a high titre (21.6 nmol/l). A diagnosis of myasthenia gravis was made based on the clinical

* *Corresponding author*. Tel.: +91 484 6655000; mobile: +91 9846010220.
E-mail addresses: shivnairmd@gmail.com, shiv.nair@rajagirihospital.com (S.K. Nair).
http://dx.doi.org/10.1016/j.ijtb.2016.01.007

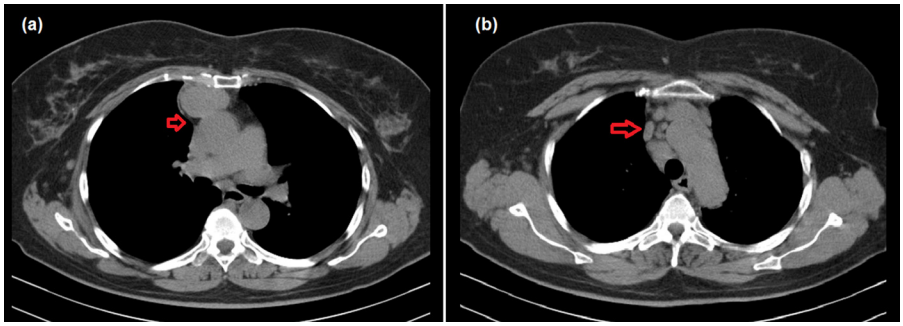


Fig. 1 – (a) Thymoma with suspected loss of fat plane between pericardium and capsule (arrow). (b) Mediastinal lymphadenopathy (arrow).

and laboratory findings. She was started on anti-cholinesterase drugs, immunosuppressants (azathioprine) and oral steroids (0.5 mg/kg) following which her clinical status improved over the next three months. However, a computerised tomography (CT) scan of thorax taken 8 weeks into therapy revealed a homogenous thymic mass [Fig. 1(a)] with a suspected loss of fat plane between the mass and mediastinal pleura/pericardium. The same scan revealed multiple mediastinal nodes [Fig. 1(b)]. Lung fields were normal with no evidence of TB-related changes. As there was no evidence of clinically significant peripheral lymphadenopathy or intra-abdominal nodes by sonography, the possibility of a lymphoma was considered unlikely. Also, her AFP and beta HCG values were normal excluding the diagnosis of a germ cell tumour. In view of the CT findings, a provisional diagnosis of an invasive thymoma was made and surgical decision for a maximal thymectomy with lymph node clearance was taken. Under general anaesthesia, a formal sternotomy was done and all the fatty tissue from the cervical region up to diaphragm and between both the phrenic nerves was excised. Thymic mass was well encapsulated with no gross infiltration into any surrounding structures [Fig. 2(a)]. Mediastinal lymph node dissection was performed [Fig. 2(b)]. She was extubated within an hour after the procedure and had an uneventful course of recovery. Histopathology report of the tumour returned Grade 2 well-differentiated thymoma [Fig. 3(c)] (WHO Type A, Masaoka Stage II). However, histopathology examination of the lymph nodes revealed acid-fast bacilli [Fig. 3(a)], multiple confluent granulomas with central caseation [Fig. 3(b)] consistent with the diagnosis of TB lymphadenitis and no evidence of any tumour dissemination. She subsequently was started on anti-tubercular therapy and is presently on follow-up. We believe, probably, the combination of long-standing diabetes and immunosuppressive therapy could have predisposed her to the tubercular infection in an endemic area like ours and resulted in this interesting diagnosis.

3. Discussion

TB presenting as isolated mediastinal mass has been reported previously.[5] MT is relatively common in developing countries with a high prevalence of TB.[4] On the contrary, this presentation is rare in the West and most often related to immunosuppression. Reactivation TB, especially in developing countries following steroid therapy, has been reported by Afridi et al.[6] The presence of myasthenia gravis-thymoma complex in conjunction with MT is a rare diagnosis, but

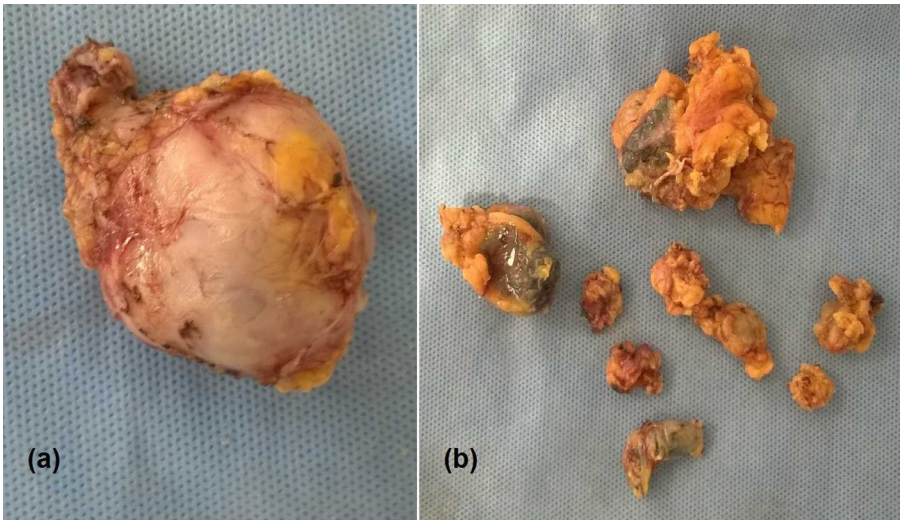


Fig. 2 – (a) Excised thymic mass. (b) Excised mediastinal lymph nodes.

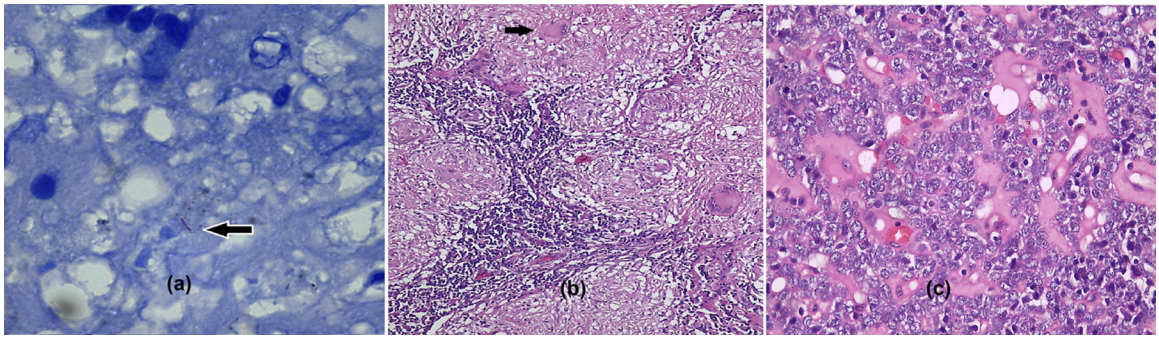


Fig. 3 – (a) Lymph node specimen with acid-fast bacillus (arrow). (b) Lymph node specimen with caseating granuloma (arrow). (c) Thymoma histopathology.

possible, considering the endemic nature of the disease in this part of the world and concurrent immunosuppression.

Nam et al.[7] reported a similar case with worsening of myasthenic symptoms and steroid-induced aggravation of MT. Another similar report from Japan documented a clinical deterioration of myasthenia gravis with MT, which simulated a recurrent thymoma.[8] Contrary to these reports, in the present case, the myasthenic symptoms improved following immunosuppression despite a subsequent diagnosis of coexistent MT.

The CT findings in the present case suggested the possibility of a malignant thymoma with the mediastinal lymphadenopathy and suspected loss of fat plane. Invasive thymoma has been described to be a homogenous tumour similar to its benign counterpart on CT in contrast to a thymic carcinoma with areas of calcification and necrosis rendering non-homogeneity on imaging.[9,10] The mediastinal lymphadenopathy, however, was singular. This favoured a provisional diagnosis of invasive thymoma, which was subsequently proved right with the histopathology finding of micro-deposits in the capsule. The diagnosis of MT was contrary to the rare but anticipated diagnosis of nodal metastasis.

Another grey area is the timing of radiotherapy in Stage II thymoma in the setting of immunosuppression and active mediastinal tuberculosis. Although there is general consensus on the need for postoperative radiotherapy in the treatment of invasive thymoma, no definite recommendations are available in the literature regarding when it needs to be initiated taking into consideration the attendant risks of immunosuppression, wound healing and an ongoing anti-tuberculous therapy.

4. Conclusion

This report, thus, suggests the need to include TB as a differential diagnosis in cases of myasthenia gravis-thymoma disease complex with mediastinal lymphadenitis especially in the setting of immunosuppression and endemicity. Active surveillance of these patients on immunosuppression for early detection of TB or its reactivation is warranted. Due consideration should be given for frozen section biopsy examination of the lymph nodes excised in such cases, to facilitate an earlier diagnosis and treatment.

Conflicts of interest

The authors have none to declare.

Acknowledgements

The authors thank Dr. Susheel Chandy, Senior Pathologist, Lisie Hospital, Cochin, Kerala, India.

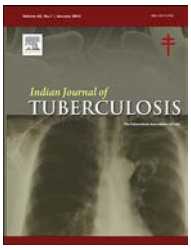
REFERENCES

1. Singh G, Amin Z, Wuryantoro. Wulani V, Shatri H. Profile and factors associated with mortality in mediastinal mass during hospitalization at Cipto Mangunkusumo Hospital, Jakarta. *Indones J Intern Med*. 2013;45:3–10.
2. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. *Autoimmune Dis*. 2011;2011:474512.
3. Monden Y, Nakahara K, Nanjo S, et al. Invasive thymoma with myasthenia gravis. *Cancer*. 1984;54:2513–2518.
4. Bloomberg TJ, Dow CJ. Contemporary mediastinal tuberculosis. *Thorax*. 1980;35:392–396.
5. Khilnani GC, Jain N, Hadda V, Arava SK. Anterior mediastinal mass: a rare presentation of tuberculosis. *J Trop Med*. 2011;2011:635385.
6. Afridi A, Labrador M, O'Rourke C, Nation J, Nathani N. Steroid related tuberculosis: does a subgroup require a more cautious approach? *Eur Respir J*. 2011;38(55):2589.
7. Nam TS, Park MS, Choi KH, et al. Myasthenia gravis aggravated by steroid-induced isolated mediastinal tuberculous lymphadenitis. *J Clin Neurol*. 2010;6:224–226.
8. Furui E, Ide Y, Takamori M. Acute deterioration of myasthenia gravis in association with tuberculous mediastinal lymphadenitis, simulating recurrence of thymoma. A case report. *Rinsho Shinkeigaku*. 1995;35:428–430.
9. Hung HC, Lee T, Lee SK. Differential diagnosis of invasive thymoma and thymic carcinoma by CT findings. *Chin J Radiol*. 1999;24:179–184.
10. Zerhouni EA, Scott Jr WW, Baker RR, Wharam MD, Siegelman SS. Invasive thymoma: diagnosis and evaluation by computed tomography. *J Comput Assist Tomogr*. 1991;15:429–433.

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Abstracts

Treatment as diagnosis and diagnosis as treatment: Empirical management of presumptive tuberculosis in India

McDowell A, Pai M. *Int J Tuberc Lung Dis*. 2016;20(4):536–543. http://dx.doi.org/10.5588/ijtld.15.0562.

Background: Mismanagement of TB is a concern in the Indian private sector, and empirical management might be a key contributor.

Objective: To understand factors associated with empirical diagnosis and treatment of presumed TB in India's private sector and examine their effects on TB care.

Design: In this ethnographic study, 110 private practitioners of varying qualifications who interacted with TB patients (90 in Mumbai and 20 in Patna) were interviewed, and a subset was observed while providing clinical care. Interviews and observations were analysed for indicators of empirical diagnosis and treatment.

Results: All non-specialist practitioners began antibiotic treatment, especially quinolones, for persistent cough before prescribing a test. Several factors contribute to empirical management. These include a common practice use of medications as diagnostic tools, a desire to provide rapid symptom relief to patients, a desire to manage illness costs effectively, uncertainty about the presentation of TB, the effects of broad spectrum antibiotics on TB symptomology, and uncertainty about the accuracy of available TB tests.

Conclusion: Empiricism in general and in TB care is widespread in the urban private sector in India. Ethnography might offer useful insights for addressing this in public–private mix models.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.002

A systematic review of economic models used to assess the cost-effectiveness of strategies for identifying latent tuberculosis in high-risk groups

Auguste P, Tsertsvadze A, Court R, Pink J. *Tuberculosis*. 2016;98 (May). http://dx.doi.org/10.1016/j.tube.2016.04.007.

Background: Timely diagnosis and treatment of latent tuberculosis infection (LTBI) through screening remains a key public health priority. Although globally it is recommended to screen people at high risk of developing TB, the economic evidence underpinning these recommendations is limited. This review critically appraised studies that had used a decision-analytical modelling framework to estimate the cost-effectiveness of interferon gamma release assays (IGRAs) compared to tuberculin skin test (TST) for detecting LTBI in high risk populations.

Methods: A comprehensive search of MEDLINE, EMBASE, NHS-EED was undertaken from 2009 up to June 2015. Studies were screened and extracted by independent reviewers. The study quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and the Philips' checklist, respectively. A narrative synthesis of the included studies was undertaken.

Results: Ten of 8793 studies were considered relevant for inclusion. Two economic evaluations were conducted in a child population, six in an immunocompromised population and two in a recently arrived population. Most studies ($n = 7$) used a decision tree structure with Markov nodes. In general, all models performed well in terms of reporting quality, but were subject to limitations to structure and model inputs. Models have not elaborated on their setting or the perspective of the studies was not consistent with their analyses. Other concerns were related to derivation of prevalence, test accuracy and transition probabilities.

Conclusion: Current methods available highlight limitations in the clinical effectiveness literature, model structures and assumptions, which impact on the robustness of the cost-effectiveness results. These models available are useful, but limited on the information that can be used to inform on future cost-effectiveness analysis. Until consideration is given on deriving the performance of tests used to identify LTBI that progresses to active TB, and the development of more comprehensive models, the economic benefit of LTBI testing with TST/IGRAs in high risk populations will remain unanswered.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.003

How do patients access the private sector in Chennai, India? An evaluation of delays in tuberculosis diagnosis

Bronner Murrison L, Ananthakrishnan R, Swaminathan A, et al. *Int J Tuberc Lung Dis*. 2016;20(4):544–551. http://dx.doi.org/10.5588/ijtld.15.0423.

Setting: The diagnosis and treatment of tuberculosis (TB) in India are characterized by heavy private-sector involvement.

Delays in treatment remain poorly characterized among patients seeking care in the Indian private sector.
Objective: To assess delays in TB diagnosis and treatment initiation among patients diagnosed in the private sector, and pathways to care in an urban setting.
Design: Cross-sectional survey of 289 consecutive patients diagnosed with TB in the private sector and referred for anti-tuberculosis treatment through a public–private mix program in Chennai from January 2014 to February 2015.
Results: Among 212 patients with pulmonary TB, 90% first contacted a formal private provider, and 78% were diagnosed by the first or second provider seen after a median of three visits per provider. Median total delay was 51 days (mean 68). Consulting an informal (rather than formally trained) provider first was associated with significant increases in total delay (absolute increase 22.8 days, 95%CI 6.2–39.5) and in the risk of prolonged delay >90 days (aRR 2.4, 95%CI 1.3–4.4).
Conclusion: Even among patients seeking care in the formal (vs. informal) private sector in Chennai, diagnostic delays are substantial. Novel strategies are required to engage private providers, who often serve as the first point of contact.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.004

Can intensified tuberculosis case finding efforts at nutrition rehabilitation centers lead to pediatric case detection in Bihar, India?

Pathak RR, Mishra BK, Moonan PK, et al. *J Tuberc Res*. 2016;4 (1):46–54. http://dx.doi.org/10.4236/jtr.2016.41006.
Introduction: Seven district-level Nutritional Rehabilitation Centres (NRCs) in Bihar, India provide clinical and nutritional care for children with severe acute malnutrition (SAM).
Aim: To assess whether intensified case finding (ICF) strategies at NRCs can lead to pediatric case detection among SAM children and link them to TB treatment under the Revised National Tuberculosis Control Programme (RNTCP).
Materials and methods: A retrospective cohort study was conducted that included medical record reviews of SAM children registered for TB screening and RNTCP care during July–December 2012.
Results: Among 440 SAM children screened, 39 (8.8%) were diagnosed with TB. Among these, 34 (87%) initiated TB treatment and 18 (53%) were registered with the RNTCP. Of 16 children not registered under the RNTCP, nine (56%) weighed below 6 kg—the current weight requirement for receiving drugs under RNTCP.
Conclusion: ICF approaches are feasible at NRCs; however, screening for TB entails diagnostic challenges, especially among SAM children. However, only half of the children diagnosed with TB were treated by the RNTCP. More effort is needed to link this vulnerable population to TB services in addition to introducing child-friendly drug formulations for covering children weighing less than 6 kg.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.005

Tuberculosis and HIV co-infection in Vietnam

Trinh QM, Nguyen HL, Do TN, et al. *Int J Infect Dis*. 2016;46 (May):56–60. http://dx.doi.org/10.1016/j.ijid.2016.03.021.
Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are leading causes of disease and death in Vietnam, but TB/HIV disease trends and the profile of co-infected patients are poorly described.
Methods: We examined national TB and HIV notification data to provide a geographic overview and describe relevant disease trends within Vietnam. We also compared the demographic and clinical profiles of TB patients with and without HIV infection.
Results: During the past 10 years (2005–2014) cumulative HIV case numbers and deaths increased to 298,151 and 71,332 respectively, but access to antiretroviral therapy (ART) improved and new infections and deaths declined. From 2011 to 2014 routine HIV testing of TB patients increased from 58.9% to 72.5% and of all TB patients diagnosed with HIV in 2014, 2803 (72.4%) received ART. The number of multidrug resistant (MDR)-TB cases enrolled for treatment increased almost 3-fold (578–1532) from 2011 to 2014. The rate of HIV co-infection in MDR and non-MDR TB cases (51/1532; 3.3% vs 3774/100,555; 3.8%; OR 0.77, 95% CI 0.7–1.2) was similar in 2014.
Conclusions: The care of TB/HIV co-infected patients have shown sustained improvement in Vietnam. Rising numbers of MDR-TB cases is a concern, but this is not ''driven'' by HIV co-infection.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.006

Experience of active tuberculosis case finding in nearly 5 million households in India

Prasad BM, Satyanarayana S, Chadha SS, et al. *Public Health Action*. 2016;6(1):15–18. http://dx.doi.org/10.5588/pha.15.0035.
In India, to increase tuberculosis (TB) case detection under the National Tuberculosis Programme, active case finding (ACF) was implemented by the Global Fund-supported Project Axshya, among high-risk groups in 300 districts. Between April 2013 and December 2014, 4.9 million households covering ~20 million people were visited. Of 350 047 presumptive pulmonary TB cases (cough of ≤2 weeks) identified, 187 586 (54%) underwent sputum smear examination and 14 447 (8%) were found to be smear-positive. ACF resulted in the detection of a large number of persons with presumptive pulmonary TB and smear-positive TB. Ensuring sputum examination of all those with presumptive TB was a major challenge.

Conflicts of interest

The authors have none to declare.

http://dx.doi.org/10.1016/j.ijtb.2016.07.007