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Clinical Profile of MDR-TB patients with special reference to kanamycin induced ototoxicity in a tertiary care hospital of eastern India

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Introduction: MDR-TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-TB drugs. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. Kanamycin, is an aminoglycoside antibiotic used to treat multi-drug resistant TB in the intensive phase. **Objective:** To analyze the patients of MDR-TB with respect to age, sex and presence of comorbidities like diabetes mellitus. Also to study the incidence of hearing impairments among patients of MDR-TB receiving injectable Kanamycin. **Methods:** 40 patients of MDR-TB diagnosed by sputum culture and drug susceptibility testing (DST) have been classified on the basis of age, sex and presence of diabetes mellitus. All have received injectable Kanamycin for 6months in their intensive phase (IP). Patients giving history of auditory impairments underwent pure tone audiometry (PTA) for detection of sensory neural hearing loss, if any. **Result:** Out of 40 patients of MDR-TB, 30 were males and the rest 10 were females. Age ranges from 12 to 70 years among which maximum patients fell in the age group of 21-30 years (12 patients). 16 patients were diabetic. After getting Kanamycin, 8 patients gave the history of auditory disturbances and only 1 patient found to have severe sensory neural hearing loss confirmed by pure tone audiometry.**Conclusion:** Prevalence of MDR-TB has been found more among males and in younger age group. Diabetes Mellitus play a major role here. Kanamycin induced hearing loss is not a very serious concern in our study.

Keywords: Deafness, Kanamycin, Pure tone audiometry, Multidrug-resistant tuberculosis

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Introduction

Multi Drug Resistant TB is often abbreviated to MDR-TB. Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most powerful, first-line anti-TB drugs [1]. MDR-TB is treatable and curable by using second-line drugs.

However, second-line treatment options are limited and require extensive chemotherapy (up to 2 years of treatment) with medicines that are expensive and toxic. For many years Multi Drug Resistant TB (MDR) has been the most basic form of drug resistant TB. In 2017, MDR-TB remains a public health crisis and a health security threat. WHO estimates that there were 558 000 new cases with resistance to rifampicin – the most effective first-line drug – of which 82% had MDR-TB [2]. The MDR-TB burden largely falls on 3 countries - India, China and the Russian Federation- which together account for nearly half of the global cases and the type of TB for which many statistics were collected [2].

There are two main ways that one can get MDR TB. Firstly one can get it if he doesn't take drugs exactly as have been instructed by health care provider. One can also get MDR if he gets TB bacteria from another person who already has MDR-TB. This is known as primary TB. It used to be believed that most people had acquired TB, but now-a-days more and more cases of primary TB have been detected. Kanamycin is an aminoglycoside antibiotic used to treat several bacterial infections. It is used to treat multidrug resistant TB as well. Kanamycin, discovered in 1957, is used as part of a treatment regimen, usually involving 5 medicines, to treat MDR TB. It is part of a group of medicines called injectable. [3,4]. Kanamycin is administered via intramuscular injection for at least six months during the intensive phase of treatment. When necessary, Kanamycin may be continued during the continuation phase, administering the same dose 2 to 3 times weekly.

Mode of action: Kanamycin is an aminoglycoside antibiotic isolated from Streptomyces kanamyceticus. Kanamycin inhibits protein synthesis by binding to the 70S ribosomal unit, making TB unable to grow.

Dosage of Kanamycin in MDR-TB[5]

16-29kg. 30-45kg. 46-70kg. >70 kg
500 mg. 750mg. 750mg. 1000mg

Side effects: Injectable including kanamycin can cause damage to the kidneys. Creatinine levels should be monitored in patients with kidney damage. Kanamycin is generally safe in patients with liver disease; however, it should be used with caution, as it may cause rapid progression of hepatorenal syndrome (kidney failure in a person with cirrhosis of the liver) in patients with severe liver disease .Kanamycin can also cause loss of hearing, dizziness, peripheral neuropathy, pain at the injection site and rashes. Kanamycin should not be taken during pregnancy, unless as a last resort, as it may cause deafness in the infant.

Objectives

1. To analyze the patients of MDR-TB with respect to age, sex and presence of comorbidities like diabetes mellitus.

2. To study the incidence of hearing impairment among patients of MDR-TB receiving injectable Kanamycin.

Methods

Study Type: Hospital based Cross-sectional Observational study.

Sample Size: Total 40 patients with MDR-TB were enrolled.

Sampling technique: Consecutive non probability technique used

Inclusion Criteria: Patient diagnosed with MDR-TB by sputum culture and drug susceptibility testing (DST). Both males and females above the age of 12 years attending OPD of Chest Medicine and District Tuberculosis Centre, Malda Medical College and Hospital.

Exclusion Criteria: 1) Patients having only Rifampicin resistance, 2) Patients of XDR-TB, 3) Patients unwilling to join the study.

Study Procedure: The study commenced after obtaining permission from Institutional Ethical Committee and written informed consent from patients. Patients were selected with a diagnosis of MDR-TB by Sputum culture and DST. A detailed history and thorough clinical examination was done.

Pure tone audiometry were performed before the start of therapy and was repeated after 2 months and 6 months of Kanamycin use to assess hearing loss due to this drug.

Place of study: a) OPD of Chest Medicine and District Tuberculosis Center, Malda Medical College and Hospital, Malda, West Bengal.

Results and Analysis

A total of 40 patients of MDR-TB who were receiving Injection Kanamycin were included in this study. The key baseline characteristics are listed in the table below:

Table-1: Age distribution among MDR-TB patients as follows

Age distribution of the patients shows that maximum number of patients are in the age group 21-30 years (30%) followed by group 31-40 years (25%).

Age in years	Number of cases	percentage (%)
12-20	4	10
21-30	12	30
31-40	10	25
41-50	8	20
51-60	4	10
61-70	2	5

Table-2: Gender distribution among MDR-TB patients as follows

Gender	Number of cases	Percentage (%)
Male	30	75
Female	10	25

Table-3: Prevalence of Diabetes Mellitus in the study group

Number of Diabetic cases	Percentage (%)
16	40

Table-4: Prevalence of Kanamycin induced auditory impairment in the study group

Number of auditory impairment cases	Percentage (%)
8	20

Table-5- Prevalence of Kanamycin induced sensory neural deafness in the study group.

Number of sensorineural deafnesscases	Percentage (%)
1	2.5

Image-1- Classification of hearing loss on the basis of pure tone audiometry: Pure tone audiometric air conduction testingis performed by presenting a pure tone to the ear through an earphone and measuring the lowest intensity in decibels (dB) at which this tone is perceived 50% of the time. This measurement is called *threshold.* The testing procedure is repeated at specific frequencies from 250 to 8000 hertz (Hz, or cycles per second) For each ear, and the thresholds are recorded on a graph called an audiogram [6].

Image-1- Classification of hearing loss on the basis of pure tone audiometry

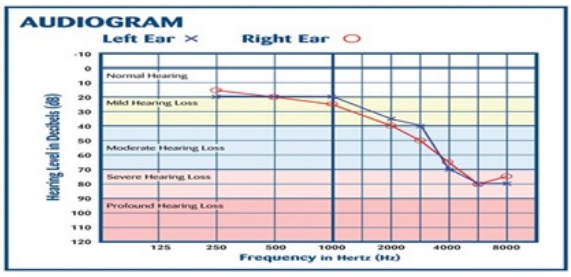

Image-2- Standard classification of hearing loss in both ears showing in Audiogram

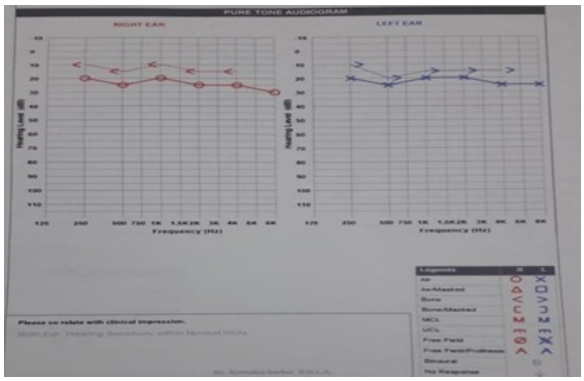

Image-3- Patient in our study group having normal Audiogram

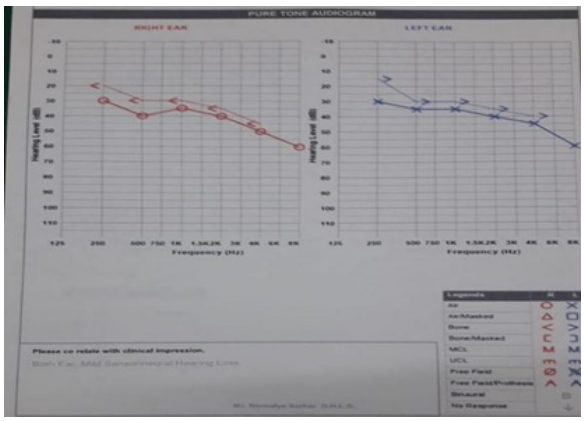

Image-4- Patient in our study group having mild auditory loss

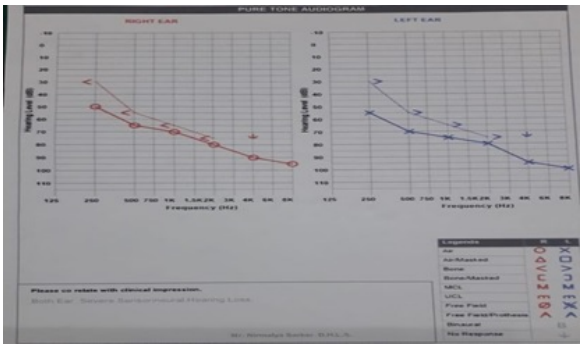

Image-5: Only patient in our study group showing sever sensoryneural hesring loss and Kanamycin had been stopped subsequently

Discussion

Our study has been compared with those of the other studies of MDR-TB and Kanamycin induced hearing impairment in various parts of the world. Analysis of the age distribution in our study showed that maximum number of patients are in the age group 21-30 years (30%) followed by group 31-40 years (25%). One study in Taiwan showed that cases above 65 years of age accounted for 27.4% (13.7%-37.1%) of the total MDR- TB cases, followed by 20.0% and 21.8% for the 55-64-year-old and 45-54-year-old age groups, respectively [7]. A study from Ahmedabad, India, in which 83.7% of patients were in age group of 16–45 years with a mean age of 33.64 ± 11.03 [8].

Gender distribution in our study is in the ratio of 3:1 for male and female. Over the past twenty years, tuberculosis (TB) case notifications among men have exceeded those among women in most settings. In 2014, the male-to-female (M:F) ratio in smear-positive pulmonary TB case notification was 1.7 globally and ranged from 1.0 in the Eastern Mediterranean Region to 2.1 in the Western Pacific Region. The excess of notified cases among men has often been explained as a result of barriers faced by women in seeking care for and being diagnosed with TB [9].

Historically, the incidence of tuberculosis in patients with diabetes has been high. In 1934, a treatise on the association between diabetes and tuberculosis was written by Howard Root (a physician at the Deaconess Hospital, Boston, MA, USA), before the availability of antimycobacterial drugs.

His lengthy tome described the epidemiology, pathology, and clinical course of dually affected patients. In his studies, tuberculosis in adults with diabetes was more common than expected, and risk was particularly high in schoolchildren and adolescents with diabetes. [10,11].

In the Philadelphia Diabetic Survey, Boucot and colleagues found a two-fold increase in prevalence tuberculosis by chest radiograph in 3106 diabetic patients compared with 70767 controls of similar demographics. Further more, they found that diabetic patients who needed more than 40 units of insulin per day were twice as likely to develop tuberculosis as those using lower doses, thus linking severity of diabetes mellitus with risk of tuberculosis. [12].

This is in accordance with our study where the prevalence of Diabetes Mellitus in MDR-TB patients where it is as high as 40%. One study in China also showed strong association between DM and MDR-TB[13] Association between diabetes mellitus and multi-drug-resistant tuberculosis has also been shown in a study conducted in Ethiopia [14]. A high proportion of individuals with multidrug-resistant tuberculosis (MDR-TB) develop permanent hearing loss due to ototoxicity caused by injectable aminoglycosides [15]. A study published in JMA also showed severe ototoxicity by Kanamycin [16].

A prospective cohort study published in European Respiratory journal by Scott K. Heysell et al in 2017 showed more than 75% patients experienced hearing loss after Kanamycin treatment whereas in our study, only 20% of patients experienced mild to moderate hearing loss and only 2.5% showed severe sensorineural deafness[17]. In our study, only 20% of patients complained about auditory disturbances among which only 1 patients found to have severe sensorineural hearing loss confirmed by pure tone audiometry.

Conclusions

- Prevalence of MDR-TB has been found more among males.
- Prevalence of MDR-TB has been found more among younger age group.
- Diabetes Mellitus has a strong association with the occurrence of MDR-TB.
- Kanamycin induced hearing loss is not a very serious concern in our study.

Outcome of this Study

Although our study shows similar prevalence of MDR-TB on age and gender basis and a higher prevalence rate among Diabetics, contrary to Internationally acclaimed studies, our study does not show a very strong association of ototoxicity among Kanamycin users.

Limitations

01. Small number of patients were included in the study.
02. Long term follow-up could not be done to evaluate ototoxicity.

Contribution by Authors

Dr Saswata Ghosh and Dr Atish Halder: Concept designing and conducting the study.

Dr ProsenjitGayen: Conducting the study and writing the manuscript.

Prof. Ramtanu Bandyopadhyay: Guiding the study procedure and preparing the manuscript suitable for publication.

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