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Ototoxic effect of anti-tubercular treatment on multi-drug resistant tuberculosis patient

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ABSTRACT

Background: Multi-drug resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs. Regimen for MDR-TB comprises of 6 drugs - kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the intensive phase and 4 drugs levofloxacin, ethionamide, ethambutol and cycloserine during the 18 months of the continuation phase. The aim of our study was to document the incidence and severity of ototoxicity in MDR-TB patient receiving category IV treatment under the revised national tuberculosis control program.
Methods: Prospective cohort study was carried out on proven case of MDR-TB patients. Total 61 patients were evaluated for the development of ototoxicity, for a period of one year. First three months of study pre-treatment baseline audiogram were recorded by pure tone audiometry, and repeat audiogram was done after six months and nine months.
Results: Out of 61 patients 21 patients developed ototoxicity with incidence of 34.42%. Incidence of high frequency hearing loss was 21.31% and flat loss was 13.11%.
Conclusions: MDR-TB patients, due to effect of aminoglycoside may develop mild to severe degree of hearing loss. As hearing loss in these patients is permanent, careful audiological monitoring should be done regularly.

Keywords: Tuberculosis, Hearing loss, Ototoxicity

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis.* Multi-drug resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs.[1] This regimen for MDR-TB comprises of 6 drugs - kanamycin, levofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine during 6-9 months of the intensive phase and 4 drugs levofloxacin, ethionamide, ethambutol and cycloserine during the 18 months of the continuation phase.

Many of the drugs used in MDR TB are toxic and have severe side effects. It is this toxicity that is the main concern in long-term administration of these aminoglycosides**.** Ototoxicity and nephrotoxicity are dose related adverse effects of aminoglycoside.[2] Different studies have reported hearing loss as an adverse drug reaction in patients with MDR-TB ranging from 6-18%.[3,4] Aminoglycosides are toxic to the cochlea by selectively destroying the basal hair cell of the basilar

membrane which is required for high frequency hearing.[5] They can also destroy the hair cells of the vestibule.[6] These drugs reacts with transition metal ions to produce reactive oxygen species (free radicals) which in turn damages the cells through an oxidative process.[5] Thus, hearing loss in those treated with aminoglycosides usually starts with the high frequency loss which later progresses to frequencies more associated with speech communications as drug exposure is continued.[7]

Aims and objective

To document the incidence and severity of ototoxicity in MDR-TB receiving category IV (CAT IV) treatment under the revised national tuberculosis program (RNTCP).

METHODS

A prospective cohort study (case series) was carried out in the Department of E.N.T. & Head and Neck Surgery, M.L.N. Medical College, Allahabad, from October 2017 to September 2018, on proven cases of MDR-TB (who were enrolled in DOTS plus CAT IV Regimen after diagnosis by cartridge based nucleic acid amplification test (CBNAAT) after due clearance from the Institutional Ethics Committee. Record of 70 patients was obtained in the first three months of study. Nine patients were lost in follow- up period, and they were excluded from the study. So, study was done on total 61 patients. Patients were properly informed about the nature of the disease and procedure to be done; consent was taken from patients before his/her participation in the study.

Inclusion criteria

All patients willing to participate in the study and eligible for CAT IV regimen were enrolled and admitted to initiation of treatment in the DOTS plus.

Exclusion criteria

Exclusion criteria were patients under 10 years of age and greater than 60 years; patients eligible for category IV regimen with pre-existing co-morbid conditions viz. Renal, hepatic, vestibular or auditory impairment, peripheral neuropathy etc; pre-existing long-standing middle ear pathology like chronic suppurative otitis media (CSOM), otosclerosis, overt congenital anomalies of external ear/ middle ear or inner ear like congenital/ hereditary hearing loss with or without syndromic abnormalities; history of hypersensitivity to aminoglycosides; significant family history to ototoxicity; prolonged use of certain drugs predisposing to aminoglycoside toxicity viz. loop diuretics, nephrotoxic drugs, muscle relaxants etc.

Patients were admitted in pulmonary medicine ward and detailed history, including screening for mental illness, drug, alcohol abuse etc. was obtained. Hematological investigations like complete blood count (CBC), liver function tests (LFT), fasting blood sugar to screen for diabetes mellitus, blood urea and serum creatinine, thyroid function test, and pregnancy test in all women in the childbearing age group. Chest x ray was also done.

Pure tone audiometry (PTA) was done in a sound treated room using a conventional audiometer with frequencies 500, 1000, 2000, 4000, 8000 Hz.

Record of 70 patients was obtained in the first three months of study. Nine patients were lost in follow- up period, and they were excluded from the study.

So, total 61 patients were evaluated for the development of ototoxicity, for a period of one year. First three months of study pretreatment baseline audiogram were recorded by PTA, and repeat audiogram was done after six months and nine months.

Hearing threshold at 500 Hz, 1000 Hz, 2000 Hz was considered as low frequency and 4000 Hz, 8000 Hz considered as high frequency. Average of low frequencies and high frequencies obtained separately. A threshold shifts greater than 10 dB in bone conduction was considered as a significant hearing loss. Threshold shift at 4000 Hz, and 8000 Hz considered as a high frequency hearing loss (HFHL) and flat loss (FLAT) when addition to HFHL threshold shift also present in lower frequencies (500 Hz, 1000 Hz, 2000 Hz).

For statistical analysis of the data we use SPSS software and test used chi–square test and z test and p value less than 0.05 was considered as statistically significant.

Categorization of hearing loss was also done according to, Hearing Disability,1995 Act, India.

Table 1: Categorization of hearing disability.

Categories	Hearing loss in dB	Speech discrimin-ation	% of impair-ment
Mild hearing loss	26-40 dB in better ear	80-100%, in better ear	<40-50
Moderate hearing loss	41-60 dB in better ear	50-80%, in better ear	40-50
Severe hearing loss	61-70 dB in better ear	40-50%, in better ear	51-70
Profound hearing loss	71-90 dB in better ear	<40%, in better ear	71-100
Total hearing loss	>90 dB	Very Poor	100

RESULTS

The present study was done in Department of Otorhinolaryngology, M.L.N. Medical College, Allahabad, during the period from October 2017 to

September 2018. The result and analysis of this study are as follows:

A total of 61 patients was taken up for the study who were proven cases of MDR-TB (enrolled in DOTS plus category IV regimen after diagnosis by CBNAAT).

In the present study most of the patients were in the third decade (40.98%) followed by the second decade (27.86%). The mean age of the study group was 27.09±8.38 years (mean±SD) with a range of 14-47 years.

In the present study, 70.49% patients were male and 29.50% patients were female. So, there was a male preponderance in the study. In the present study, 88.52% (n=54) patients of rural and 11.47% (n=7) patients of urban back ground. In male, 90.69% (n=39) of rural and 9.30% (n=4) of urban background. In female patients, 83.33% (n=15) patients of rural background and 16.66% (n=3) of urban background.

Incidence of hearing loss in patients on CAT IV anti-tubercular treatment

From Table 2 it was observed that out of 61 patients after 9 months from the beginning of CAT-IV anti-tubercular treatment (ATT) significant threshold shift in bone conduction (>10 dB) was observed in 21 patients (34.42%), according to programmatic management of drug-resistant tuberculosis (PMDT) guideline.

Age wise distribution of patients having ototoxicity

In our study it was observed that maximum cases with hearing loss were in 31-40 years of the age group (38.00%), while the age group of 11-20 years and 21-30 years were equally affected (23.80%) and patients in age group of 41-50 years were least affected (14.28%) group. But it was also observed that patients of 41-50 year and 31-40 year age group had the greatest proportion of hearing loss of 60% and 57.41% respectively as compared to younger age groups. Although correlation of age with ototoxicity did not reach statistically significant at 95% confidence interval (CI) and 5% level of significance (p=0.067476).

In our study ototoxicity was observed in 21 patients at end of nine months. Out of 21 patients 18 (85.71%) patients experienced bilateral hearing loss, while only 3 (14.28%) patients experienced unilateral hearing loss.

Table 2: Incidence of ototoxicity (n=61).

Hearing loss*	Patients on cat IV ATT				
	After six months	%	After nine months	%	Incidence
>10 dB shift in bone conduction	18	29.50	21	34.42	34.42/100
<10 dB shift in bone conduction	43	70.49	40	65.57	
Total	61	100	61	100	

*Hearing loss: >10 dB shift in bone conduction considered as significant.

Table 3: Distribution of patients having ototoxicity according to affected frequencies on audiogram (n=61).

	High frequency hearing loss (4000 & 8000 Hz)	%	Flat loss hearing loss at both speech and high frequency (500 to 8000 Hz)	%	Total
No of patients affected	13	21.31	8	13.11	21

Table 4: Distribution of patients on the basis of threshold shift at different frequencies on audiogram.

Threshold shift in bone conduction [in dB] *	Low frequency (500, 1000, 2000 Hz)		High frequency (4000, 8000 Hz)	
	N	%	N	%
0-10	108	88.52	83	68.03
11-20	9	7.37	22	18.03
21-30	3	2.45	12	9.83
31-40	1	0.81	4	3.27
41-50	1	0.81	1	0.81
Total	122	100	122	100

Distribution of patients having ototoxicity according to affected frequencies on audiogram

From Table 3 it was observed that out of 61 patients hearing loss was observed in 21 patients and out of 21 affected patients only high frequency hearing loss was present in 13 patients (21.31%) and 8 patients (13.11%) experienced hearing loss at both speech and high frequencies (flat loss).

Distribution of patients on the basis of threshold shift at different frequencies on audiogram

From Table 4 it was observed that at low frequency 88.52%ears have normal hearing threshold while 11-20 dB threshold shift seen in 7.37% of ears. 2.45% of ears develop threshold shift of 21-30 dB, while 31-40 dB and 41-50 dB threshold shift seen in only 0.81% of patients. At high frequency 68.03% ears have normal hearing threshold while 11-20 d B threshold shift seen in 18.03% of ears. 9.83% of ears develop threshold shift of 21-30 dB, and 31-40 dB threshold shift seen in 3.27% of patients, while 41-50 dB threshold shift seen in only 0.81% of patients.

Table 5: Comparison of average of air conduction threshold at low frequencies (500, 1000, 2000 Hz) after six and nine months (n=61).

	Mean air conduction	Standard deviation (SD)	Z value
Pre treatment	19.12352	2.876095	
After six months	23.98074	7.917797	4.506
After nine months	25.54656	7.95922	5.932

Comparison of average of air conduction and bone conduction threshold at low frequencies (500, 1000, 2000 Hz)

From Table 5 it was observed that after six months and nine months of treatment value of Z is 4.506 and 5.932 respectively which is higher than critical value (1.96), i.e. difference in mean air conduction is highly significant. It was also observed that there was statistically significant shift occurred in air conduction of testing population (n=61) at low frequency after six months and nine months from initiation of CAT-IV ATT.

From Table 6 shows that after six months and nine months of treatment value of Z are 5.686 and 6.867 respectively which are higher than critical value (1.96). So observed difference is highly significant. It is observed that there was statistically significant shift occurred in bone conduction of testing population (n=61) at low frequency after six and nine months from initiation of CAT-IV ATT.

Table 6: Comparison of average of bone conduction threshold at low frequencies (500, 1000, 2000 Hz) after six and nine months (n=61).

	Mean bone conduction	Standard deviation (SD)	Z value
Pre treatment	10.69484	2.542911	
After six months	15.75016	6.476738	5.686
After nine months	17.04385	6.75878	6.867

Comparison of average of air conduction and bone conduction threshold at high frequencies (4000, 8000 Hz)

Table 7 shows that after six and nine months of treatment value of Z is 5.932 and 7.292 respectively which is higher than critical value (1.96). So observed difference is highly significant. It is observed that there was statistically significant shift occurred in air conduction of testing population (n=61) at high frequency after six and nine months of CAT-IV ATT.

Table 7: Comparison of average of air conduction threshold at high frequency (4000, 8000 Hz) after six and nine months.

	Mean air conduction	Standard deviation (SD)	Z value
Pre treatment	19.65164	2.826154	
After six months	28.38115	11.16148	5.932
After nine months	30.76492	11.5637	7.292

Table 8: Average of bone conduction threshold at high frequency (4000, 8000 Hz) after six and nine months (n=61).

	Mean bone conduction	Standard deviation (SD)	Z value
Pre treatment	11.29098	3.001955	
After six months	18.96852	8.858859	6.411
After nine months	21.12287	10.0632	7.313

From Table 8 shows that after six and nine months of treatment value of Z is 6.411 and 7.313 respectively which is higher than critical value (1.96). So observed difference is highly significant. It is observed that there was statistically significant shift occurred in bone conduction of testing population (n=61) at high frequency after six and nine months of CAT-IV ATT.

Categorization of patients for hearing loss according to, Hearing Disability, 1995 Act, India

Table 9 represents that out of 61 patients only 10 patients develop hearing impairment at speech frequency which is 16.39%. Out of 61 patients 8 patients (13.11%) develop mild hearing loss. One patient develops moderate hearing loss (1.6%) and one patient develops severe hearing loss.

Table 9: Categorization of hearing loss of total 61 patients according to, hearing disability, 1995 Act, India.

Category	Type of impairment	Hearing loss in dB	No of patients having hearing impairment	%
	Normal hearing	<26 dB in better ear	51	83.60
I	Mild hearing loss	26-40 dB in better ear	8	13.11
II(a)	Moderate hearing loss	41-60 dB in better ear	1	1.6
II(b)	Severe hearing loss	61-70 dB in better ear	1	1.6
III(a)	Profound hearing loss	71-90 dB in better ear	0	
III(b)	Total hearing loss	>90 dB	0	

DISCUSSION

Tuberculosis (TB) has existed for millennia and remains as a major global health problem. Long-term treatment of MDR-TB often results in the development of side effects that affect the patient's health condition. The treatment of drug-resistant TB necessitates the use of second-line injectable anti-TB drugs which are associated with hearing loss. The aminoglycoside group is the major drug group which is used in the treatment of patients with MDR-TB and can leads to irreversible hearing loss, so use of aminoglycosides is itself troublesome in MDR-TB patients.

The present prospective cohort study was done on 61 MDR-TB patients with a range of 14-47 years of age group with a mean age of 27.09±8.3 (Age±SD) years of age. Most of the patients were 21-30 years of the age group (40.98%) followed by 11-20 years of the age group (27.86%) which was similar to study done by Tiwari et al and patients was younger in other study.[2,8,9]

Maximum cases of ototoxicity were observed in the age group of 31-40 years (38%) while the age group 11-20 years and 21-30 years as similar distribution of ototoxicity of 23.80% followed by 41-50 years of age (14.28%). This distribution of ototoxicity was similar to other study.[8,10] Although the proportion of hearing loss was higher in the age group 41-50 years (60%) followed by 31-40 years (57.41%) which was similar to other study.[2,10,11]

In our study 70.49% of patients were male, and 29.50% patients were female, similar to other studies[2,8,9] while, Sharma et al did not found any significant association of ototoxicity with sex.[10]

In our study 88.52% patients belongs to rural background while 11.47% were from urban background, similar study done by other.[9,10] We did not found statistically significant association of residential distribution with hearing loss ($p>0.05$) while Sharma et al found statistically significant association of hearing loss with rural background and low socioeconomic status ($p<0.05$).[10]

In our study, out of 61 patients 21 patients developed ototoxicity with incidence of 34.42% at the end of the study. Incidence of high frequency hearing loss (HFHL) was 21.31% and flat loss was 13.11%. Our incidence of ototoxicity is comparable with a study done by Tiwari et al who reported ototoxicity in 37% of patients. Our results were contradictory to study done by Ibekwe et al, who reported incidence of ototoxicity very high in 61% of patients with high frequency hearing loss in 35.7% and flat loss in 25% of patients.[8,12] Smaller sample size of 28 patients may be limitation of their study.

In our study, out of 21 patients who developed ototoxicity, 18 patients (85.7%) had a bilateral hearing loss while only 3 patients (14.28%) developed unilateral ototoxicity. Our results were comparable with other study.[8,10,12]

From Table 4 we consider 61 patients as 122 ears and observed that threshold shift in bone conduction at end of study was 11-20 dB in7.37% ears (n=9) at low frequency and 18.03% ears (n=22) at high frequency.21-30 dB shift seen in 2.45% (n=3) ears at low frequency and 9.83% ears (n=12) at high frequency. 31-40 dB shift seen in 0.81% (n=1) ears at low frequency and 3.27% ears (n=4) at high frequency.41-50 dB shift seen in 0.81% (n=1) ears at low frequency and 0.81% ears (n=1) at high frequency. 88.52% ears (n=108) at low frequency and 68.03% ears (n=83) at high frequency showed negligible (0-10 dB) shift in bone conduction. Our study was unique in this sense as to our best knowledge so far there is no study which mentions such categorization of threshold shift.

We also observed that at the end of study there is highly significant shift in air conduction and bone conduction at both low and high frequencies of whole study population from pretreatment level ($Z>1.96$). It signifies the effect of CAT-IV ATT on hearing.

At the end of our study we, categorize hearing impairment of total 61 patients (according to, Hearing Disability, 1995 Act, India). We observed that only 16.31% have hearing impairment at speech frequency, while 83.60% have no hearing impairment. Out of this 16.31% patients 13.31% patients develop mild degree of hearing impairment while 1.6% patients developed moderate hearing impairment and equal number (1.6%) of patients developed severe degree of hearing impairment at speech frequency. It has been noted that loss at 4000 Hz can affect communication when there is background noise even though it is not a speech frequency.[13] This shows that there is a high level of affectation of patient's speech and communication with the use of second line of medication. Despite of this, Kanamycin is still commonly used in clinical settings like ours (in developing countries) for MDR-TB where cost considerations are a major factor in patient compliance.[9]

Monitoring of hearing after the baseline has been recommended 1-2 times per week for patients receiving ototoxic antibiotics.[13] However, we were not able to do repeated PTA twice weekly in the present study because of the costs involved and the inability of patients from distant neighborhoods to report twice a week at our center where facilities for conventional assessment of hearing are available. It is not common to find equipment for audiometry as well as trained staff at peripheral centers in a developing country like ours. We used conventional frequency range (250–8000 Hz) audiometer in our study as only conventional audiometers with frequency range between 125 and 8000 Hz are available with us, owing to low cost compared to high frequency equipment.

Protection against ototoxicity may be achieved by reducing the availability of iron using chelators, such as deferoxamine and dihydroxybenzoate. This may lead to a dramatic reduction of aminoglycoside ototoxicity. Importantly, these iron chelators do not interfere with the therapeutic efficacy of the aminoglycosides. Other drugs of this class are aspirin and D-methioninas has shown protection against amikacin induced ototoxicity.[7,14]

CONCLUSION

In our study we concluded that the effect of aminoglycoside on hearing in patients receiving second line ATT is a serious challenge, as there is a high prevalence of MDR-TB in our environment. The high frequency hearing loss was most common hearing impairment in MDR-TB patients, followed by hearing impairment across all frequencies. 10 dB to 50 dB shift seen in bone conduction after nine months of CAT-IV ATT. Patients on CAT-IV ATT may develop mild to severe degree of hearing loss and daily conversation ability of the patient may be reduced. Patients may be hearing handicap. As patients on CAT-IV ATT may develop hearing loss, only at high frequency they may experience difficulty in communication when there is background noise. As hearing loss in these patients is permanent, careful audiological monitoring should be done regularly. Early identification of ototoxicity and the institution of another regime may be done. Ototoxicity may be also reduced by use of otoprotective agents.

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REFERENCES

1. World Health Organization. Guidelines for the programmatic management of drug resistant tuberculosis – Emergency update. WHO/HTM/ TB/2008.402. Geneva: WHO; 2008.
2. de Jager P, van Altena R. Hearing loss and nephrotoxicity in long term aminoglycoside treatment in patients with tuberculosis. Int J Tuberc Lung Dis. 2002;6(7):622-7.
3. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis. 2004;8(11):1382-4.
4. Brock Biology of Microorganisms. In: Madigan M, Martinko J, Parker J, eds. 10th ed. Pearson Education, 2002.
5. Selimoglu E. Aminoglycoside‐induced ototoxicity. Curr Pharm Des. 2007;13(1):119-26.
6. Guthrie OW. Aminoglycoside induced ototoxicity. Toxicology. 2008;249(2-3):91-6.
7. Rybak LP, Ramkumar V. Ototoxicity. Kidney Int. 2007;72(8):931-5.
8. Tiwari M. Roy AK. Shamliya K. Yadav SK. Ototoxicity Associated With The Usage Of Injectable Kanamycin In Multi-Drug Resistant Tuberculosis Patients during Intensive Phase Of Category IV Treatment On DOTS-Plus Therapy. IOSR J Dent Med Sci.2016;15(2):12-6.
9. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7(1):5.
10. Sharma V, Bhagat S, Verma B, Singh R, Singh S. Audiological Evaluation of Patients Taking Kanamycin for Multidrug Resistant Tuberculosis. Iran J Otorhinolaryngol. 2016;28(86):203-8.
11. Gatell JM, Ferran F, Araujo VE, Bonet M, Soriano E, Traserra J, et al. Univariate and multivariate

analyses of risk factors predisposing to auditory toxicity in patients receiving aminoglycosides. Antimicrob Agents Chemother. 1987;31(9):1383-7.
12. Ibekwe MU, Nwosu C. Pure tone audiometric findings in patients on second-line treatment for multidrug-resistant tuberculosis. Port Harcourt Med J. 2016;10(3):97-101
13. Fausti SA, Helt WJ, Gordon JS, Reavis KM, Philips DS, Konard DL. Audiologic monitoring for ototoxicity and patient management. In: KCM Campbell. Pharmacology and ototoxicity for audiologists. New York: Thomson Delmar Learning. 2007.
14. Campbell KC, Meech RP, Klemens JJ, Gerberi MT, Dysstad SS, Larsen DL, et al. Prevention of noise- and drug induced hearing loss with D-methionine. Hear Res. 2007;226(1–2):92-103.

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