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ORIGINAL ARTICLE

Ototoxic Hearing Loss in the Multidrug Resistant Tuberculosis

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ABSTRACT

Background: The recommended treatment of MDR TB lasts for 20 months following therapy with second line anti-tuberculosis drugs (SLDs) which carry the risk of adverse effects including hearing loss. The objective of this study was to determine the frequency of hearing loss and its association with demographic and clinical variables in multidrug resistant tuberculosis patients on second line drugs.

Methodology: This cross-sectional study was carried out at the Audiology Department of the Civil Hospital Bahawalpur, over a period of 6 months, from 1st May 2019 to 31st October 2019. The study included 65 diagnosed cases of tuberculosis, aged 12-70 years, of either sex, who were on second line antituberculous therapy. Non-probability purposive sampling technique was used for patient selection. Screening was performed using medical history sheet, otoscopy and hearing assessment. Data was entered and analyzed using SPSS- Version 21.

Results: Among a total of 65 patients,43 (66.2%) were males and 22(33.8%) were females. Mean age of study population was 35.87±9.35 years. Hearing loss was seen in 14(21.5%) cases, with mild hearing loss in 15.4% cases and moderate hearing loss 6.2%. Hearing loss was associated with type of drug used, its duration and associated symptoms of tinnitus and vertigo (p=0.000).

Conclusion: It was found that hearing loss is quite frequent (21.5 %) with multidrug resistant anti-tuberculous therapy in this region and is significantly associated with the type of drug used and its duration. Majority of affected cases were seen with the use of streptomycin.

Keywords: Aminoglycosides, Hearing loss, Multi-drug resistant tuberculosis, Ototoxicity, Tuberculosis

Authors' Contribution:
[1]Conception; Literature research; manuscript design and drafting; [2,] Critical analysis and manuscript review; [3] Data analysis; [4]Manuscript Editing.[5,6]

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Introduction

Normal hearing is the mainstay of human communication, in the absence of which an individual can suffer from serious loss in social, psychological and professional life.[1] In developing countries like Pakistan, tuberculosis including multi-drug resistant tuberculosis (MDR-TB) is on the rise. MDR-TB is an aftermath of a strain of Mycobacterium tuberculosis (MTB) which develops resistance to at least two of the most powerful anti TB drugs i.e., isoniazid (INH) and rifampicin (RMP).[2] An Ethiopian study revealed that TB infected cases do not disclose their condition to their relatives, thus contributing to development of MDR-TB.[3] The level and prevalence of ototoxicity due to anti-tuberculosis therapy (ATT) for MDR-TB has not been fully evaluated because of lack of ototoxicity monitoring.[4] MDR-TB being resistant to rifampicin and isoniazid, is a growing clinical and health problem with high prevalence of adverse events.[5,6] Drugs used for treatment of MDR-TB are often very

toxic with 62% patients having residual side effect at the end of treatment. These may be gastrointestinal and psychiatric problems, arthralgia, central nervous system complications, hearing and balance issues, neuropathy of peripheral nerves, menstrual disturbances, liver, ophthalmic, kidney and thyroid problems in decreasing order of frequency, with hearing loss being an important issue.[7-9]

According to a WHO report in 2020, approximated TB prevalence was 5.8 million with majority of cases reported in South-East Asia.[10] The estimated incidence of TB in India was found to be approximately 2.79 million with 40% of population infected with Tuberculous bacilli.[11] High prevalence of MDR-TB has also been reported from Central Asian region.[10] Noncompliance to ATT in our country and neglect are resulting in MDR TB with a high prevalence of 69% in patients reporting to tertiary care centers in Pakistan.[12]

With the resurgence of tuberculosis and the prevalence of MDR-tuberculosis in Pakistan[4], the emphasis has shifted to treatment using second line drugs, which carry the risk of adverse effects like hearing loss (HL).[13] The present study was thus conducted to determine the prevalence of hearing loss and its association with demographic and clinical variables in MDR-tuberculosis patients using second line drugs.

Methodology

This cross-sectional study was conducted in the Audiology department of the Civil Hospital, Bahawalpur, from May 1, 2019 to October 31, 2019. In total 65 diagnosed cases of tuberculosis, both genders, aged 12 to 70 years and on 2nd line anti-tuberculosis therapy (ATT) were included in the study. Patients were recruited using non-probability purposive sampling technique. Cases with symptoms of ear disease prior to administration of ATT, with incomplete data or cases in which tests could not be conducted because of any reason were excluded from the study. Sample size was calculated using the formula $N= z^2a/2xpx(1-p) \times DEFF/d,^2$ taking a prevalence of MDR TB as 4.6% [14], estimated effective size (DEFF) of 1, at level of confidence of 95% and 5% absolute precision.

Participants were screened using medical history sheet, ear examination and hearing assessment. All cases were diagnosed by medical specialist. History was taken in a confidential setting and included questions regarding auditory and vestibular disorders with presence of vertigo, tinnitus, and exposure to agents harmful to hearing such as occupational or leisure noise and ototoxic drugs. Hearing of all cases was assessed by pure tone audiometer Model Audio LAB V-3. Both ears were tested using the method of ascending pure tones at frequencies of 0.25, 0.5, 1, 2, 4, 6, 8 and 16 kHz before descending to 1 and 0.5 kHz. Hearing measurements were performed in a soundproof audiometry booth that met the American National Standards Institute (ANSI).[15]

Data was entered and analyzed using SPSS - version 21. Mean and percentages were calculated. Chi-square test was used to observe association of hearing loss with demographic and clinical variables. Variables included for association with HL were age, gender, associated symptoms, ototoxic drugs administered, drug duration and smoking. P value of < 0.05 was considered statistically significant.

Results

Among total of 65 cases, Hearing loss (HL) was seen in 14 (21.5%). Demographic and clinical characteristics revealed that 43(66.2%) were males and 22(33.8%) were females with a male to female ratio of 1.95:1 (table 1). Majority of patients, 26(40%) were between 31-40 years of age. There was no significant association of HL with gender (*p* value: 0.149) and age (*p* value: 0.069). There was however significant association of HL with associated symptoms (p=0.000) with 6 out of 8 cases of vertigo having HL and 4 out of 8 cases of tinnitus having HL. A significant (p=0.000) association of HL was also observed with drug used, it

was found that 28(43.1%) cases in whom Amikacin was used there was no HL while out of the 13(20%) cases in which streptomycin was used, 11 developed HL. Moreover, only one case out of 12(18.5%) in which both amikacin and streptomycin were used developed HL.

HL was also significantly associated with duration of drug use, with HL noted in 2 out of 2 cases at 2 months duration, and 6 out of 10 cases at 8 months duration, while only 4 out of 32 cases and 2 out of 21 cases developed HL at 6 and 7-months duration respectively, indicating that the drug actually caused HL at initiation of treatment.

The study, however, revealed no significant association of HL with smoking. With reference to frequency of degree of HL of both ears, the sample population revealed a similar picture with 10(15.4%) cases with mild HL and 4 (6.2%) cases with moderate HL in both ears. The remaining sample did not reveal any HL. As far as configuration of audiogram was concerned, a flat curve was noted in 6 (9.2%) of right ears and 8 (12.3%) of left ears, while high frequency steeply sloping audiogram was noted in 5(7.7%) of right and 6(9.2%) of left ears. Mean hearing threshold of cases which developed HL, increased from 26.43 ±15.86 dB to 35.36 ± 16.34 dB from 250 Hz to 8 KHz for right ear and from 26.78+12.18 to 37.50 ± 12.36 dB from 250 Hz to 8 KHz for left ear. However, the difference of mean thresholds at each frequency from 250 to 8 kHz from both ears was not significant (table III).

Table I: Demographic and Clinical Characteristics: Descriptive Statistics. (n=65)

VARIABLE			HEARING STATUS		
Category	**Characteristics**	**n (%)**	**Normal n=51**	**Affected n=14)**	**X^2 P-Value)**
Age Group	10-20	3 (4.6)	1	2	8.71 (0.069)
	21-30	16 (24.6)	12	4	
	31-40	26 (40)	24	2	
	41-50	16 (24.6)	12	4	
	51-60	4 (6.2)	2	2	
Gender	Males	43 (66.2)	36	7	2.08 (0.149)
	Females	22 (33.8)	15	7	
Assoc. Symptoms	No	49 (75.38)	45	4	23.53 (0.000)
	Vertigo	8 (12.31)	2	6	
	Tinnitus	8 (12.31)	4	4	
Drugs	Amikacin	28 (43.1)	28	0	36.69 (0.000)
	Streptomycin	13 (20)	2	11	
	Both Amikacin & Streptomycin	12 (18.5)	11	1	
	Others	12 (18.5)	10	2	
Drug Duration (Months)	2	2 (3.1)	0	2	19.38 (0.000)
	6	32 (49.2)	28	4	
	7	21 (32.3)	19	2	
	8	10 (15.4)	4	6	
Smoking	Yes	10 (15.38	8	2	0.02 (0.898)
	No	55 (84.62)	43	12	

Table II: Characteristics of Hearing Loss. (n=65)

VARIABLE		FREQUENCY	
Group	**Characteristics**	**(n)**	**%**
HL	Normal Hearing	51	78.5
	Hearing Loss	14	21.5
	mild	10	15.4

Degree of HL Right Ear	moderate	4	6.2
	Normal	51	78.5
Degree of HL Left Ear	mild	10	15.4
	moderate	4	6.2
	Normal	51	78.5
Configuration Audiogram Right Ear	Flat Curve	6	9.2
	High Frequency steeply Sloping Curve	5	7.7
	Total	11	16.9
Configuration Audiogram left Ear	Flat Curve	8	12.3
	High Frequency steeply Sloping curve	6	9.2
	Total	14	21.5
Duration of HL	No hearing Issue	50	76.9
	2-Months	4	6.2
	3-Months	4	6.2
	4-Months	3	4.6
	5-Months	4	6.2

Table III: Hearing Threshold and Paired Sample t-test Statistics. (N=14)

EAR	FREQUENCY	RANGE	MIN.	MAX.	MEAN	SD
Right	250Hz	60	10	70	26.43	15.86
	500Hz	65	10	75	28.21	17.82
	1KHz	55	15	70	30.71	15.67
	2KHz	55	15	70	32.14	14.77
	4KHz	55	20	75	33.57	14.99
	8KHz	60	15	75	35.36	16.34
Left	250Hz	40	10	50	26.78	12.18
	500Hz	35	15	50	28.93	12.58
	1KHz	45	10	55	30.00	12.25
	2KHz	35	20	55	33.57	12.62
	4KHz	45	10	55	35.36	12.47
	8KHz	50	10	60	37.50	12.36

	Paired Differences				
Frequency	**Mean**	**SD**	**Std. Error Mean**	**T-Value**	**P-Value**
Right Ear - Left Ear					
250 - 250	0.23	8.72	1.08	0.21	0.83
500 - 500	0.38	9.93	1.23	0.31	0.76
1000 - 1000	0.31	8.79	1.09	0.28	0.78
2000 - 2000	-0.62	8.64	1.07	-0.57	0.57
4000 - 4000	-0.69	10.49	1.30	-0.53	0.60
8000 - 8000	-0.08	11.09	1.38	-0.06	0.96

Discussion

Aminoglycosides are responsible for permanent HL, which affects quality of life with susceptibility of patients varying significantly. Hence, ways to identify high-risk cases are essential so that protective strategies and alternate treatment may be considered.[16] The present study revealed a prevalence of HL of 21.5% (n=14) among MDR-TB cases on ototoxic ATT. Results of a study from Sogebi *et al* are comparable to our results with 22.9% cases of MDR-TB patients showing HL.[17] In another study conducted by Bhardwaj *et al*. prevalence of side effects of MDR-TB was 83.33% of which HL was present in 22%.[7] In contrast Haris *et al*. in a study conducted at Cape Town, reported a high prevalence of aminoglycoside induced HL of 57% [18] and Saqwa *et al*. reported a prevalence of 58%.[19]

In our study, we found no significant association of HL with gender (p=0.149). However, Nhokwara et al and Sogebi OA et al reported significant association

of HL with gender, with males more frequently affected than females.[19,20] The mean age of our study population was 35.87 ±9.35 years with maximum cases of HL noted in the age group 21-30 and 41-50 years however the age association was not statistically significant (*p*=0.069). In contrast, in a study by Nhokwara et al, a statistically significant increase in cases of HL was noted with increasing age.[19]

In our study, 8 cases developed tinnitus and 8 cases reported vertigo and there was a significant association of HL with these associated symptoms (*P*=0.000). While in another study, 36% cases reported associated symptoms of vertigo and tinnitus, with the most common symptom being tinnitus in 75% of the cases.[21] A significant (*p*=0.000) association of HL was also noted with drug used, with higher frequency of HL due to streptomycin. Another study, using kanamycin for MDR TB, reported 75% of cases with HL.[22] Amikacin is an important part of Botswana's MDR-TB treatment, recommended by WHO in most countries. A study by Modongo C et al reported an increase in the risk of HL as the duration and dosage per weight per month increased.[23]

The current study revealed, a significant association (*p*=0.000) with higher frequency of cases affected at 2 months and at 8 months. More than one mechanism is responsible for this, including higher doses, genetic idiosyncrasy, and ischemia resulting in early HL .[24]Jayakumar et al noted no HL before two months, while 27% & 20% cases in right and left ear developed HL at 2 months and 39% & 27 % developed HL at 3 months.[21] Similarly, in another study, 22% cases developed HL at 2 months.[22] Sogebi et al also reported that, ototoxicity with HL developed with treatment from 4 to 17 (Mean 9.4 ± 3.4) weeks with the use of aminoglycosides.[17]

Saqwa *et al.* in a comparative study between amikacin and kanamycin, reported higher and more severe HL in cases of Amikacin.[20] In another study, 55% developed ototoxicity and this was 5 times more likely to develop with amikacin compared to capreomycin.[25] This finding was in contrast to our study, where streptomycin was the major culprit. This indicates that in addition to the ototoxic drug, certain risk factors might be involved resulting in inconsistent results in different studies.

Regarding degree of HL in both ears, 10 (15.4%) cases reported mild HL and 4 (6.2%) moderate HL in both ears. In contrast, a study by Jayakumar et al, mild HL was reported in 75% cases, moderate in 9.1%, moderately severe HL in 9.1%, severe HL in 4.5% and profound HL in 2.3% cases.[21] Saqwa et al reported severity of HL with 32% having mild HL, 23% moderate, 16% moderate to severe, 10% severe and 15 with profound HL. [20]. In another study, prevalence of mild HL was 58.1%, moderate HL 30.6% and severe loss was seen in 11.3% cases.[19]

In the current study both ears revealed increase in mean thresholds from 250 Hz to 8 kHz, however the difference between right and left ear was not significant. However, according to a study reported by Jayakumar et al, ototoxic HL in MDR-TB involving both ears was present in 63.63% cases, and unilateral involvement in 36.36% cases.[21]

Current study revealed flat HL in 9.2% & 12.3% right and left ears respectively, while steeply sloping high frequency loss was noted in 7.7% & 9.2% of right and left ears respectively. However, HL was more frequently seen at higher frequencies but in 30.5%, it occurred at ≤ 2000 Hz.[22] In contrast in a study by Sogebi et al ,out of 16 cases who developed HL, 7 (43.8%) developed low frequency HL while high frequency loss was noted in 4 (25%) cases.[17] A much higher percentage of high frequency HL of 57% was noted in a study by Harris et al with higher prevalence in HIV positive cases.[18] This indicates that the frequency and level of HL is inconsistent with studies, again indicating some risk factors might be responsible.

According to Sogebi et al, age, diabetes mellitus, retroviral status were all significantly associated with HL, while gender, previous drug regimen failure showed no association with HL.[17] Some studies have

also reported association of HIV positive status, and low body weight with HL.[18.20]

Considering the results of various studies, it is suggested that a control audiogram at the initiation of the treatment for MDR-TB followed by an audiogram every month for six months and then three monthly till treatment is completed is essential for prevention and mitigation of HL associated with ototoxic ATT, and is recommended for all cases of MDR-TB.[21]

Limitation of Study: Our Study had the limitation of a small sample size with only one audiologist to perform the testing.

Conclusions

Frequency of hearing loss with multidrug resistant tuberculosis treatment was high and significantly associated with the drug used, its duration. Majority of cases were observed with use of streptomycin.

DISCLAIMER

This research is part of the main research of M Phil (Hearing sciences) thesis project.

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