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Audiological monitoring of patients undergoing multidrug resistant tuberculosis treatment at Jigme Dorji Wangchuk National Referral Hospital and Gidakom Hospital, Bhutan

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ABSTRACT

Background: Hearing impairment due to ototoxicity is one common cause adding to global burden of disability. Amikacin and kanamycin are two common Aminoglycosides used to treat multidrug resistant tuberculosis which results in ototoxicity. The mean prevalence rate of multidrug resistant tuberculosis in Bhutan stood at 16%.
Objective: The study is aimed to establish prevalence rate of hearing impairment due to ototoxicity and secondary side effects which may ascertain specific early intervention.
Method: A total of 42 Patients undergoing multidrug resistant tuberculosis treatment participated in the study conducted at Jigme Dorji Wangchuk National Referral Hospital and Gidakom Hospital over a period of one year. Audiological tests were conducted once every month. The severity of ototoxicity was being graded using Brock's hearing loss grades.
Result: The study found 45.23% participants with some degree of hearing loss consequent to multidrug resistant tuberculosis treatment. Around 9.5% of the total participants developed potential disabling hearing loss. Around 30.09% of participants had experienced subjective tinnitus during the course of treatment. Study found no significant association (p-value 0.88, 95%CI 0.93–1.00) between referred test result of DPOAE (distortion product Otoacoustic emission) screener and the ototoxicity.
Conclusion: Study showed with significant prevalence of ototoxicity. Since hearing impairment have negative impact on psychosocial wellbeing and communication abilities, it is paramount importance to put in place the various preventative measures. With current guidelines by World Health Organisation on replacement of second-line injectable by oral regimens while treating patients with MDR-TB, it is expected to address ototoxicity and related issues.

1. Introduction

Globally, an estimate of 10.0 million people developed TB in 2019 and Geographically, majority of people were in the WHO regions of South-East Asia with 44% [1] of the total. There is urgent need to pronounce and address these increase to reach the 2022 targets on quality care and preventive treatment that were set in the political declaration of the UN high-level meeting [2].

Total of 206 030 people with MDR/RR-TB were detected in 2019 globally, an increase of 10% from 186 883 in 2018 [1]. Multi drug resistant tuberculosis (MDR-TB) refers to the condition when TB is found resistant to treatment with first line of anti-tuberculosis drugs such as rifampicin and isoniazid [3]. Addressing MDR-TB as public health crisis was listed among five priority actions required to accelerate the progress towards 2015 targets while combating TB [4].

Treatment of MDR-TB with aminoglycoside is known to cause organ specific degenerations and ototoxicity is one form of it. Aminoglycoside ototoxicity erodes and degenerates outer hair cells of cochlea causing symmetrical progressive and irreversible sensory hearing loss [5].

Ototoxicity for patients with MDR-TB treatment in India was charted at 27.0% suggesting a promising need for addressing this issue [6]. Similar study conducted in Nigeria found that 54.6% developing with varying degrees of hearing loss due to ototoxicity during MDR-TB treatment [7]. WHO, while addressing the rising prevalence of hearing

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loss in 2018 validated that figures from aminoglycosides induced hearing loss reported from different parts of the globe falls between 10 and 50% [8].

In Bhutan, it was found that the mean prevalence rate of MDR-TB was 16%. The burden of primary MDR-TB and secondary MDR-TB is higher in Bhutan (primary 13% and secondary −35%) than other South East Asian countries (Primary −2.7% and secondary −13%) and globally (Primary − 3.5% and secondary 18%) [9].

Global burden of disease study found hearing loss as fourth leading cause of disability [10]. More than 5% of global population (360 million people) are currently living with disabling hearing loss [11]. Annual cost of unaddressed hearing loss stands between $750–790 billion globally posing substantial costs to the health-care system and to the economy as a whole [11]. Approximately 90% of people living with moderate to profound hearing impairment reside in low- and middle-income countries [12] where strategies to address hearing care faces huge obstacles.

DPOAE (Distortion-product Otoacoustic emissions) demonstrated a decreased amplitude in the frequencies $>$ 3 kHz ($P < 0.05$) which appeared to be more sensitive in detection of cochlear damage than pure-tone audiometry [13] while study by Reavis, K.M., et al. [14] found it low effective over PTA (pure tone audiometry). However, the study by Konrad martin, D et al. [15] recommends more studies on reliable sample size to validate the use of OAE in the early detection of ototoxicity. Since PTA is subjective and DPOAE is objective test, the correlation and comparison of these two results may help in early identification of ototoxicity.

This study is first of its kind in Bhutan aimed to ascertain the magnitude of hearing damage during MDR-TB treatment.

2. Objectives

It is aimed to determine the prevalence rate of hearing impairment due to ototoxicity and its secondary side effects among participants who did not have any form of hearing loss before MDR-TB treatments using aminoglycosides which may ascertain specific early intervention. This study will further validate if the DPOAE screening test is effective and accurate in an early detection of ototoxicity.

3. Methods

3.1. Study design and participation

This is a longitudinal cohort study. A total of 46 patients aged between 15 and 65 years diagnosed with MDR-TB at Jigme Dorji Wangchuk National Referral Hospital and Gidakom Hospital at Thimphu, Bhutan who consented to participate were included for the study. The study was conducted over a period of one year (September 2018 to August 2019).

3.2. Study variables and measures

MDR-TB treatment with Kanamycin of 15 mg per kg once a day except Sundays in combination with daily dose of ethhionamide, ethambutol, pyrazinamide and cycloserine were administered by the physician during hospital stay. Hospital stay duration varied from 3 to 4 months until culture conversion where first culture tested negative.

The study excluded all the patient with evidence of any types and degrees of hearing loss during baseline audiometry since the objective of this study was to rule out potential damage to normal hearing candidates during the treatment. However, patients with no responses in three frequencies at puretone audiometry test during MDR-TB treatment were included as participants to validate with ASHA (American Speech and hearing association) third criteria of ototoxicity. Thus, 4 patients were excluded for the purpose of this study.

PTA is subjective hearing test to detect the hearing thresholds whereas DPOAE screening test is an objective hearing test. DPOAE was administered to validate if it's absolute result can be used to detect early onset of ototoxicity as some studies have found it to be more sensitive to cochlear damage.

Baseline PTA using Harp Inventis diagnostic audiometer test and DPOAE screening test using Otoread interacoustics were being performed by Audiologists in sound treated room at Audiology unit, JDWNRH on their first visit. The first visit was the day when the patient had been admitted for treatment of MDR-TB. Patients receiving second line treatment of MDR-TB at Gidakom hospital were escorted by nurse on duty to reach at JDWNRH for monthly follow up. The total visits recorded for each participant varied from 3 to 6 times as some of the participants had been discharged before 6 months after their culture conversion. Since noise has proven to deteriorate high frequency hearing loss which exacerbate ototoxicity effect [16] and effect of noise increases with the increase in the exposure duration [17], the participants were counselled on limiting noise exposure in any forms.

The study analysis is based on the American Speech and Hearing Association (ASHA) criteria for ototoxicity[(a) $>$ 20 dB pure-tone threshold shift at one frequency, (b) $>$ 10 dB shift at two consecutive test frequencies, and (c) loss of response at three consecutive frequencies where responses were previously obtained]. Thus, any participants detected with either one of the above criteria or combination of any two or all criteria is considered as developing ototoxicity.

As the ASHA criteria include confirmation of test results and relies on thresholds obtained on repeated tests than results obtained on a single test [18], the data collected focused on retest measurements. The severity of ototoxicity is graded using the Brock grading system which is a 5-point rating scale which grades hearing loss progression from high to lower frequencies [19] as shown in Table 1.

3.3. Statistical analysis

Descriptive analyses are presented using frequencies and percentages to determine the prevalence. Logistic regression is being used to evaluate the statistically significance between OAE (Otoacoustic Emission) and ototoxicity. Statistical significance was defined as $p < 0.05$. All statistical analyses were conducted using SPSS software, version 26.

3.4. Ethical concern

The study was conducted with prior approval from research Ethical Board of Bhutan. An informed written consent was obtained from the patients to participate in the study. Since no invasive procedures were involved in the study, age below 18 had no relative issues providing the consent.

4. Results

4.1. Demographic characteristics

The total participant for the study was 42 of which 52.4% were female as shown in the Table 2. Higher percentage of participants were represented from the age group of 15 to 25 years. The mean age of the participants is 28.32.

Table 1
Brock's hearing loss grade.

Grade	Frequencies
Grade 0	All frequencies $<$ 40Db
Grade 1	$>$40 dB loss at 8 kHz
Grade 2	$>$40 dB loss at 4 kHz and 8KHz
Grade 3	$>$40 dB loss at 2KHz, 4kHZ and 8KHz
Grade 4	$>$40 dB loss at 1KHz,2KHz, 4kHZ and 8KHz

Table 2
Number and percentage of participants by gender and age group.

Gender (N = 42)	Number	Percent
Female	22	52.4
Male	20	47.6
Age Group (N = 42)		
15 – 25	26	61.9
26 – 35	8	19.0
36 – 45	3	7.1
46 – 55	3	7.1
56 – 65	2	4.8

4.2. Prevalence of ototoxicity

The study found that the incidence of reduced hearing thresholds due to ototoxicity consequent to multidrug resistant tuberculosis treatment was 45.2% by using ASHA criteria for ototoxicity. The prevalence of ototoxicity among the female participants is recorded at 28.6% compared to 16.7% for male. Considering the age group, it concluded higher prevalence rate among the age group of 15 to 25 years as shown in Table 3.

Using the ASHA criteria for ototoxicity, the prevalence is found to be 45.2% for the first criteria, 38.1% for second and 4.8% for the third. The study found out that 13 of 19 had ototoxicity in both the ears and only 6 of them developed unilateral ototoxicity as shown in the Table 3.

The onset of ototoxicity varied across the participants. 50% of the onset was in second visit which is after one month from the start of the drugs. 22.2% of the onset was during the third visit followed by 11.5% and 16.7% in fourth and fifth visit respectively.

Considering Brock's hearing loss grades, almost two third of the total having ototoxicity (63.2%) falls under grade one as illustrated in Table 4. It is found that 21.1% of the total having ototoxicity falls under grade 4 which indicates a disabling hearing loss requiring amplification by hearing aids.

4.3. Prevalence of tinnitus

The study found that 31.0% of participants experienced tinnitus during the course of treatment out of which 7 had ototoxicity as well as detailed out in Table 5.

4.4. Association between ototoxicity and DPOAE

This study found the risk of ototoxicity among the participants with absent DPOAE (43.8%) and present DPOAE (53.9%). There is no significant association (p-value 0.88, 95%CI 0.93–1.00) between the results of DPOAE screener and the ototoxicity. DPOAE was absent in 16 of the total participants out of which 7 had hearing loss due to ototoxicity (Table 6).

Table 3
Number and percentage of participants with Ototoxic induced by gender and age group.

Characteristics (N = 42)	Number	**Percent**
Ototoxic-Induced (using ASHA criteria)	19	45.2
Gender		
Female	12	28.6
Male	7	16.7
Age Group		
15 – 25	12	28.6
26 – 35	3	7.1
36 – 45	1	2.4
46 – 55	1	2.4
56–65	1	2.4
Ototoxicity (N = 19)		
Ototoxicity at both the ears (bilateral)	13	68.4
Ototoxicity unilateral ears	6	31.6

Table 4
Number and percentage on the prevalence of ototoxicity using ASHA's criteria and Brock's grading.

ASHA Criteria (N = 42)	**Number**	**Percent**
1st criteria of ototoxic Induces at shingle shift of > 20 dB	19	45.2
2nd criteria of ototoxic Induces at Consecutive Shift > 10 dB	16	38.1
3rd criteria of ototoxicity (NR at 3 frequencies after drugs)	2	4.8
Brock Grade (N = 19)		
Grade 0 (All frequency < 40 dB)	19	100.0
Grade 1 (>40 dB at 8khz (ACR&ACL).	12	63.2
Grade 2 (>40 dB at 4khz and above).	8	42.1
Grade 3 (>40 dB at 2khz and above).	5	26.3
Grade 4 (>40 dB at 1khz and above)	4	21.1

Table 5
Number and percentage on the prevalence of Tinnitus.

Characteristics	Number	Percent
Ototoxicity among experienced Tinnitus (n = 13)	7	53.9
Tinnitus (N = 42)		
Gender		
Female	6	14.3
Male	7	16.7
Age Group		
15 – 25	6	14.3
26 – 35	2	4.8
36 – 45	1	2.4
36 – 45	1	2.4
46 – 55	1	2.4
56–65	2	4.8
Experienced Tinnitus from the total sample (N = 42)	13	31.0

Table 6
Ototoxicity among the DPOAE participants.

DPOAE	No Ototoxicity	Ototoxicity	Total	OR	P-value	95% CI
Absent	9	7	16	0.91	0.879	0.93–1.00
Present	14	12	26			

5. Discussions

Drugs which have organ specific toxicity are widely used in the developing world without audiological monitoring. Epidemiological data on ototoxic deafness are lacking for developing countries [20]. There are countable studies reporting in Southeast Asia region and this study is first of its kind exploring the issue in the Himalayan Kingdom of Bhutan.

This study found out that the prevalence of hearing loss due to MDR-TB ototoxicity is 45.2% slightly lower compared to study conducted by Sagwa, E L et al. (56%) [21] and Rama L et al. [22] (47%). However, the prevalence is higher (18.7%) compared to the findings of M Sarkar et al. [23]. Furthermore, this study found 9.5% had developed severe disabling hearing loss with 68.4% bilateral sensorineural hearing loss coherent to study conducted by Sagwa, E L et al. [21] (10% of severe loss with 83% bilateral in nature). However, the absolute numbers of participants in study are small whilst percentages may be high.

The overall prevalence of ototoxicity for female participants is 28.6% compared to 16.7% for male. This study found that the prevalence of ototoxicity among the female (54.5%) is higher compared to male (35.0%). Considering the age group, it is found slightly higher among the age group of 15 to 25 years and it could be due to higher representative in the study by this age group.

During the course of treatment, 31.0% of the participants had subjective experience of tinnitus which is slightly lower compared to the study by Rama L et al [22] (42%).

Absolute result of DPOAE was pass in 53.9% of cases even when they had evidence of ototoxicity. Thus, this study found DPOAE screener is

neither sensitive nor specific for ototoxicity detection which is coherent to the study conducted by Reavis, K.M., et al. [14] and contrasting with the study conducted by Stavroulaki, P., et al., [24]. However, the variation in the findings could be due to differences in the equipment, OAE parameters, and statistical methods [15].

Studying the result of DPOAE screening test without comparing the change in total emission level was to validate if DPOAE screening test can be used by any health professionals other than audiologists whose knowledge on judging total emission level is limited. Thus, relying on the absolute final result of the DPOAE screening test as pass/refer was given importance. However, relying on absolute final results, DPOAE screening test result was found less sensitive in an early detection of ototoxicity.

Most of the participants who experienced ototoxicity varied in its onset and the interventions taken were reduction of kanamycin dose into three times a week for mild degree of hearing loss. If hearing loss exceeded moderately severe to severe degree, complete stoppage of kanamycin was adopted by the treating physician.

From 2019, WHO recommended the use of oral regimens replacing the second-line injectables (SLI) while treating patients with MDR-TB. This important WHO guideline is expected to address ototoxicity and related issues.

This study strongly suggests that the National tuberculosis Programme in Bhutan should adopt all oral regimens for MDR-TB treatment which may reduce the need of audiological assessment. In case if use of second-line injectable (SLI) is the only option, patients need audiological monitoring for early intervention if hearing loss is detected.

6. Limitations

One of the limitations of this study is being not able to conduct any hearing assessment after the completion of the MDR-TB treatment to consider the change in hearing threshold. Similarly, this study could not consider the well-established methods with high frequency audiometry range between 10000 Hz and 20000 Hz to detect the ototoxicity at the earliest [25] due to lack of commercial equipment. Furthermore, the change in total emission level of the DPOAE reading was not studied which might have increased the value of early detection of ototoxicity and could be used in setting where audiologists are available.

7. Conclusion

Administering aminoglycoside during the treatment of MDR-TB is known to have organ specific toxicity. The ototoxicity is one form where problem ranges from permanent disabling hearing loss to temporary tinnitus. The degree of hearing loss varies among individuals but the common effect is seen at higher frequencies with bilateral impairment. Hearing impairment imposing negative impact on psychosocial and communication wellbeing of a person; various actions such as putting preventive measures and interventions in place with early identification is crucial.

This study found that the prevalence of ototoxicity among MDR -TB treatment patients is quite high and almost one fourth of the participants developed potential disabling hearing loss.

CRediT authorship contribution statement

Pelden Wangchuk: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Tika Ram Adhikari:** Data curation, Investigation, Methodology, Resources, Validation, Writing - review & editing. **Gaki Nima:** Data curation, Investigation, Methodology, Resources, Validation, Writing - review & editing. **Phuntsho Dendup:** Formal analysis, Data curation, Investigation, Methodology, Resources, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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