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Original Article

Risk Factors For Treatment-Induced Hearing Impairment: Perspective From A Resource-Poor African Setting

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Abstract

Background - *Treatment-induced hearing impairment can result from prolonged administration of potentially ototoxic medications often in the pharmacotherapeutic management of chronic illnesses such as drug-resistant tuberculosis. Whereas drug ototoxicity may be idiosyncratic, it is imperative to be aware of its potential risk factors while treating patients. We aimed in our study to identify risks factors for hearing impairment in patients treated for drug-resistant pulmonary tuberculosis at our Centre.*

Patients and methods – *This study was a 24-month prospective study of drug-resistant tuberculosis patients treated at the pulmonology unit of Federal Medical Centre, Owerri, Nigeria. Each patient had pure tone audiometry before commencement of treatment (baseline) and after three months of treatment for comparison. Clinical data was obtained using pre-tested examiner-administered questionnaire. Data collected was analyzed with SPSS version 25.0 and statistical significance set at $p < 0.05$.*

Results - *Thirty-eight (38) participants completed the study with a male-to-female (M:F) ratio of 1.53:1. The modal age group was 41-50 years and median duration of presenting complaints 9.9 weeks. HIV sero-prevalence was 18.4% among the study participants. The baseline prevalence of hearing impairment was 73.7% but increased to 89.5% after three months of treatment with a cumulative incidence of 15.8% which was statistically significant ($p < 0.001$). The identified risk factors for hearing impairment were age (>50 years), family history of hearing impairment, kanamycin administration and BMI <18.5kg/m^2.*

Conclusion – *Kanamycin was associated with more severe hearing impairment than capreomycin. Advancing age, family history of hearing impairment and BMI < 18.5kg/m^2 were risk factors for development of hearing impairment in patients treated for drug-resistant tuberculosis in our setting.*

Introduction

Treatment–induced ototoxicity is a well described entity in contemporary medical practice. It is sometimes a source of dilemma as Physicians, in the line of their duty may have to choose the therapeutic benefit of potentially ototoxic medications over their undesired side effects. The rationale for this decision while being that benefit outweighs risk, can in certain instances be due to lack of other viable alternatives. One of such situations is perhaps, in the treatment of drug-resistant tuberculosis in resource-poor settings where certain parenteral aminoglycosides are typically used alongside other medications to achieve cure. These peculiar settings are rife in developing countries of which Nigeria is notably one. World Health Organization (WHO) statistics reveal that multidrug-resistant tuberculosis accounted for 4.3% of all tuberculosis cases in Nigeria in 2015 [1]. These cases require aggressive treatment often with initial hospital admission and administration of injectable aminoglycosides with ototoxic potentials such as amikacin, kanamycin and capreomycin [2,3]. There are questions on the role of co-morbidities, demographic characteristics, biophysical and physiologic profile and choice of medication among others, on the extent of ototoxicity [4,5].

The study was based in Federal Medical Centre, Owerri, South-East Nigeria. By global standards, the Centre can be described as resource-poor, being one of only two tertiary level healthcare facilities in a province of about 3.9 million people and population density of about 710 people per square kilometer [6]. The WHO Global Health Workforce Statistics in 2018 reports that Nigeria has 0.4 Physicians per 1,000 people [7].

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We describe our experience with treatment of drug-resistant tuberculosis at our Centre. Typically, this variety of tuberculosis is treated at our facility with kanamycin or capreomycin alongside oral medications like moxifloxacin, clofazimine, prothionamide, pyrazinamide, ethambutol and isoniazid.

It is established medical knowledge that aminoglycosides have ototoxic potentials especially when administered in high doses or for a prolonged duration [5,8]. We, in this study aimed to identified the factors if any, that increase the risk of hearing impairment while on treatment for drug-resistant tuberculosis with second line drugs.

Methodology

This study was a prospective evaluation of consecutive eligible and consenting patients enrolled for treatment of drug-resistant tuberculosis. Each participant had baseline (pre-treatment) pure tone audiometry performed before commencement of treatment. This was repeated after 3 months of treatment. Clinical data including biodata, medical history, medications administered and biophysical indices were obtained and analyzed.

The patients were administered one intramuscular aminoglycoside (kanamycin or capreomycin) in addition to six oral medications: prothionamide, ethambutol, isoniazid, clofazimine, pyrazinamide and moxifloxacin.

Significant audiometric changes was determined using the ASHA 1994 criteria [9]. Clinical data was obtained using pre-tested examiner-administered questionnaires. Data collected was analyzed with SPSS version 25.0. Assessment of risk factors for hearing impairment was done using logistic regression analysis. Statistical significance was set at $p < 0.05$.

All participants consented in writing to be part of the study. Ethical approval was obtained from the ethical clearance committee of the Hospital. The study spanned 24 months (April 2019 to March 2021).

Results

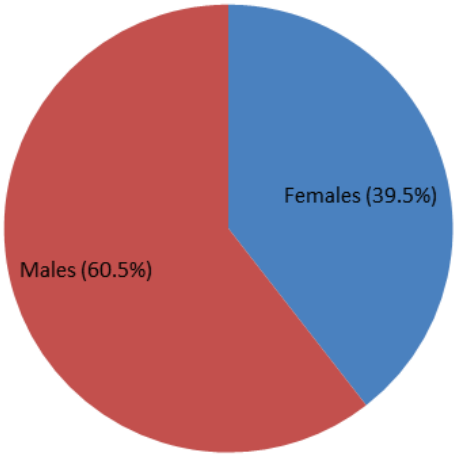

Figure 1. *Sex distribution of study participants.*

Table 1. *Demographic characteristics of study participants.*

Age (years)	Male	Female	Total (%)	p-value
11-20	1	0	1(2.6)	0.153
21-30	2	3	5(13.2)	
31-40	4	1	5(13.2)	
41-50	9	3	12(31.6)	
51-60	1	6	7(18.4)	
61-70	2	1	3(7.9)	
71-80	3	1	4(10.5)	
>80	1	0	1(2.6)	
Total	23	15	38(100.0)	

Table 2. *Clinical profile of study participants.*

Clinical feature	Response	n(%)	p-value
Prior TB treatment	Yes	15(39.5)	0.192
	No	23(60.5)	
Family history of hearing impairment	Yes	8(21.1)	0.183
	No	30(78.9)	
Presence of co-morbidity	Yes	15(39.5)	0.957
	No	23(60.5)	
HIV status	Negative	31(81.6)	0.630
	Positive	7(18.4)	
Medication administered	Kanamycin	19(50.0)	0.319
	Capreomycin	19(50.0)	

Table 3. *Prevalence of hearing impairments among study participants.*

Time of Audiometry	**Classification of Audiogram**		
	Normal (%)	Abnormal (%)	Total (%)
Baseline	10 (26.3)	28 (73.7)	38 (100.0)
Cumulative incidence over 3 months	6 (15.8)		
Third month	4 (10.5)	34 (89.5)	38 (100.0)
"Cumulative incidence by the third month = 15.8% 'Abnormal' refers to audiometric threshold >25dB in at least one ear.			

Table 4. *Comparison of baseline and third month mean pure tone averages.*

	AIR CONDUCTION			**BONE CONDUCTION**		
		Mean PTA values	p-value		Mean PTA values	p-value
Right	Baseline PTA	32.6±8.4	<0.001	Baseline PTA	25.7±8.2	<0.001
	Third month PTA	49.8±17.9		Third month PTA	42.9±16.9	
Left	Baseline PTA	32.9±8.0	<0.001	Baseline PTA	27.2±7.8	<0.001
	Third month PTA	50.8±19.1		Third month PTA	43.4±17.2	

Table 5. *Comparison of bone conduction hearing level of participants on Capreomycin vs Kanamycin.*

	BASELINE			**THIRD MONTH**		
RIGHT	Capreomycin Group (n=19)	Kanamycin Group (n=19)	p-value	Capreomycin Group (n=19)	Kanamycin Group (n=19)	p-value
NORMAL	5 (26.3)	15 (78.9)	0.112	1 (5.3)	6 (31.6)	0.027
MILD	13 (68.4)	4 (21.1)		5 (26.3)	5 (26.3)	
MODERATE	1 (5.3)	0 (0.0)		10 (52.6)	4 (21.0)	
SEVERE	0 (0.0)	0 (0.0)		3 (15.8)	1 (5.3)	
PROFOUND	0 (0.0)	0 (0.0)		0 (0.0)	3 (15.8)	
LEFT	Capreomycin Group (n=19)	Kanamycin Group (n=19)	p-value	Capreomycin Group (n=19)	Kanamycin Group (n=19)	p-value
NORMAL	5 (26.3)	15 (78.9)	0.113	1 (5.3)	5 (26.3)	0.029
MILD	13 (68.4)	4 (21.1)		4 (21.0)	6 (31.6)	
MODERATE	1 (5.3)	0 (0.0)		8 (42.1)	5 (26.3)	
SEVERE	0 (0.0)	0 (0.0)		6 (31.6)	1 (5.3)	
PROFOUND	0 (0.0)	0 (0.0)		0 (0.0)	2 (10.5)	

Table 6. *Risk factors for development of hearing impairment among participants.*

Clinical predictors	p-value	*OR	+95%CI	
			Lower limit	Upper limit
Age > 50 years	0.048	4.71	1.52	8.24
Sex	0.472	1.63	-2.46	2.83
Duration of Presenting complaints	0.106	1.46	-3.35	3.07
Family history of hearing impairment	0.017	6.47	5.13	7.39
Prior history of [a]TB treatment	0.152	1.14	-2.07	3.89
Presence of co-morbidity	0.262	1.24	-3.24	3.97
[b]HIV status	0.558	1.71	-4.21	6.32
Kanamycin administration	0.007	8.27	7.26	9.17
[c]BMI <18.5km/m^2	0.024	5.3	2.81	7.17

*OR = Odds ratio; +95%CI = 95% Confidence interval; [a]TB = Tuberculosis; [b]HIV = Human Immunodeficiency Virus; [c]BMI = Body Mass Index.

Discussion

Thirty-eight (38) participants completed the study with a male-to-female (M:F) ratio of 1.53:1, similar to ratios in studies by Sogebi et al (M:F=2:1) [10], Ibekwe et al (M:F=1:1) [11], Ramma and Ibekwe (M:F=1:1.04) [12] and Vasconcelos et al (M:F=2:1) [13]. Most participants were young, being within the 41-50 years age group and comparable with report from a population-based study of 5,684 tuberculosis patients by Zhang et al. [59] Slightly lower mean age was recorded in similar studies by Ramma and Ibekwe (33.0 years) [12], Duggal et al (39.9 years) [15] and Sogebi et al (34.5 years) [10]. The median duration of presenting complaints prior to onset of the study was 9.9 weeks (IQR 5.0-16.5). This relatively long period underscores the chronic nature of tuberculosis as well as perceived late presentation peculiar to resource poor settings such as ours. In addition, drug resistant cases sometimes were hitherto drug-susceptible and treated elsewhere before presentation at our facility.

Human Immunodeficiency Virus (HIV) positivity prevalence of 18.4% was recorded in this study, comparable with values found by Sogebi et al (13.6%) [10] in South-West Nigeria and by Akpaka et al (11.6%) [16] in Jamaica but much lower than the 46.9% reported by Sagwa et al [17] in Namibia. The different figures may highlight the variation in HIV prevalence among the populations.

The baseline prevalence of hearing impairment among our study participants was 73.7%. This represents the proportion of participants whose audiometric hearing threshold fell short of 25dB in at least one ear [18]. By the third month of follow up, the corresponding figure was 89.5% inferring a 15.8% cumulative incidence of hearing impairment which was statistically significant ($p < 0.001$). It would appear the study had a relatively high baseline prevalence of hearing impairment but this did not necessarily translate to disability as only 8 subjects (21.1%) self-reported hearing difficulty at the start of the study. The proportion of participants who self-reported hearing impairment rose to 16 (42.1%) after 3 months of treatment which was significant. Sogebi et al in South-West Nigeria found similar prevalence (78.8%) among 132 drug-resistant tuberculosis patients [10]. Conversely, slightly lower prevalence (61%) was recorded by Ibekwe and Nwosu in South-South Nigeria after 3 months of treatment with majority of participants (94%) having bilateral sensorineural hearing loss [11]. This suggests that continued treatment with second line anti-tuberculosis medication may lead to more patients developing hearing impairment.

Comparing the audiometric patterns of participants who had capreomycin with those who received kanamycin, we observed capreomycin apparently caused more of moderate and severe hearing impairments whereas kanamycin was linked with profound hearing impairment recorded in a total of 5 ears (6.6%). We infer that kanamycin may have more ototoxic potential than its counterpart, capreomycin. In similar studies comparing their ototoxic effects, kanamycin was noted to cause more severe forms of ototoxicity than capreomycin [15,19]. Similar but slightly higher proportions of profound hearing loss was recorded by Ibekwe and Nwosu (7.2%) [11] and Sagwa et al (15.0%) [17] whereas Sogebi et al [10] did not record any profound hearing loss in their study.

The risk factors for hearing impairment was assessed using multivariate logistic regression analysis and age (>50 years), family history of hearing impairment, kanamycin administration and baseline body mass index (BMI <18.5kg/m2) were found to pose significant risk. HIV sero-status, gender, duration of presenting complaints and presence of co-morbidities were not found to be significant risks. It is possible that development of hearing impairment may be multifactorial as various authors have identified varied and sometimes contrasting factors. Low baseline body weight (40-50kg) was identified as significant risk by Sagwa et al [17]. Considering that doses of injectable medications are weight-adjusted, it can be assumed that body mass index rather than merely weight may be a more appropriate measure to consider when assessing risk for ototoxicity. Sturdy et al [20] and Peloquin et al [21] found that older patients were more at risk of ototoxicity while on treatment with second line anti-tuberculosis medications. This subset of the population, apparently have diminishing ability to effectively metabolize drugs, increasing their risks

of aminoglycoside ototoxicity. Sogebi and co-workers [10], Vasconcelos et al [13] and Sagwa et al [17] all identified male gender as being at higher risk of hearing impairment while on treatment with second line anti-tuberculosis medications. It is not exactly clear what the role of gender is in ototoxicity. It could be linked to certain social behaviours such as cigarette smoking and alcohol consumption which are considered predominant among the male gender in some societies [22,23]. Conversely, their observations may be due to skewness of data as male gender was significantly predominant in their studies. Male gender was not observed to confer significant risk in our study despite slight male preponderance. HIV sero-positivity was reported as a risk factor in studies by Snow and colleagues [24] and Sagwa et al [17] although these researchers did not indicate the stages of HIV infection, viral load or CD4 count. This is particularly pertinent as patients concurrently on antiretroviral and anti-tubercular medications may be at higher risk than those who are not [25,26]. We did not find significant risk for development of hearing impairment among HIV sero-positive participants in our study although they made up only 18.4% of our sample size. Similarly, Modongo et al in Botswana [27]. Ramma and Ibekwe in South Africa [12] as well as de Jager and Van-Alterna in Netherlands [28] did not find sero-positivity related risk in their respective studies despite working on a sizeable number of patients.

Other risk factors highlighted by various authors include diabetes mellitus and smoking by Snow et al [24], cumulative dosing of drugs by Peloquin et al [21] and decreased renal function by Sturdy et al [20]. Overall, there may be a longer list of possible risk factors for development of hearing impairment while on treatment with potentially ototoxic medications and this domain is worthy of further research.

Conclusion

This research concludes that:

1. Kanamycin is likely to cause more severe hearing impairment than capreomycin.
2. Advancing age, family history of hearing impairments and BMI < 18.5kg/m^2 were risk factors for development of hearing impairment in patients treated for drug-resistant tuberculosis in our setting.

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