

Audiometric Profile of Patients on Treatment for Drug-Resistant Pulmonary Tuberculosis in Owerri, South-East Nigeria.

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Abstract

Background: Tuberculosis is an existential medical challenge in certain parts of the world necessitating global efforts. Perhaps more challenging is the treatment of drug-resistant forms of the disease as this requires use of second line drugs, predominantly potentially ototoxic aminoglycosides. The hearing impairment so caused, besides constituting social disability, can impair compliance and have far-reaching consequences. This study aimed at assessing the hearing patterns of patients on treatment for drug-resistant pulmonary tuberculosis to determine if, and to what extent their treatment affected their hearing status.

Patients and method: The study was an 18-month prospective analysis of consecutive newly diagnosed drug-resistant pulmonary tuberculosis patients in a tertiary hospital in Owerri, Nigeria. Baseline audiometry was conducted on the patients with subsequent monthly audiometry for 3 months during treatment. A control group drawn from normal population and matched for age and sex with the study group was recruited and audiometry performed on the participants in similar pattern. The audiometric patterns of both groups were analyzed and compared using Statistical Package for Social Sciences (SPSS) version 20.0 software for Windows. Statistical significance was set at $p < 0.05$.

Results: Thirty-eight (38) patients treated for drug-resistant pulmonary tuberculosis completed the study alongside thirty-eight (38) control subjects with M:F ratio was 1.53:1. The baseline prevalence of hearing impairment of any sort was 73.7% and 68.4% among the test and control groups respectively, whereas after three months it was 89.5% and 68.4% respectively. The cumulative incidence of hearing loss over three months was 15.8% and 0% respectively. This difference was statistically significant.

Conclusion: Treatment of drug-resistant tuberculosis with second line drugs can lead to significant hearing impairment within the first three months of treatment.

Keywords: Drug-resistant, Tuberculosis, Ototoxic, Audiometry, Owerri.

INTRODUCTION

Pulmonary tuberculosis, a chronic infectious disease caused by *Mycobacterium tuberculosis*, still poses an existential medical challenge in some regions of the world, requiring concerted global effort to contain. The disease is of public health concern and so was its enormity, that it was the first infectious disease to be declared a global health emergency by the World Health

Organization (WHO) [1]. Statistics by the WHO notifies that in 2015 there were about 10.4 million new cases of tuberculosis worldwide with six countries accounting for two-thirds of this global burden; of these, Nigeria ranks fourth after only India, Indonesia and China [2]. Worldwide, there were an estimated 480,000 new cases of multi-drug resistant tuberculosis in 2015[1]. There were about 586,000 tuberculosis sufferers in Nigeria with as much as 29,000 of them having drug-resistant form of the disease [3]. Tuberculosis is considered drug-resistant if there is resistance to one or more anti-tuberculosis drugs. Multi-drug resistant tuberculosis (MDR-TB) is a form of the disease in which the mycobacterium strain is resistant to at least rifampicin and isoniazid [4]. The treatment of drug-resistant tuberculosis is peculiar as it requires a relatively prolonged therapy with multiple drugs, some (such as Kanamycin, Amikacin and Capreomycin) with ototoxic potentials [5,6]. Hearing impairment developed while undergoing treatment for drug-resistant tuberculosis with aminoglycoside agents can constitute social disability and lead to poor compliance and possibly, litigation [7]. It is therefore, wholesome practice to embrace the policy of baseline and periodic audiometric assessment of patients on treatment for drug-resistant tuberculosis.

Our study aimed at assessing the audiometric patterns of patients on treatment for drug-resistant tuberculosis at our centre with specific objectives of identifying treatment-induced hearing impairment if present, and comparing the patients' hearing pattern with that of untreated control models.

METHODOLOGY

The study was a prospective, comparative analysis of consecutive newly-diagnosed drug-resistant pulmonary tuberculosis patients in Federal University Teaching Hospital, Owerri, Nigeria; a tertiary hospital with dedicated unit for treatment of tuberculosis in the region. A control group drawn from apparently normal population and matched for age and sex with the drug-resistant test group was also studied during the period. Each participant was followed up for a total of three months during which they had baseline and subsequently, monthly pure tone audiometry.

Excluded subjects include patients on treatment for other medical conditions with potentially ototoxic drugs, younger children or patient who could not co-operate appropriately with pure tone audiometry and patients who declined consent. For the control group, individuals taking potentially ototoxic medications were excluded from the study.

The patients were administered weight-appropriate intramuscular Kanamycin (Km) or Capreomycin (Cm) in addition to oral Moxifloxacin (Mfx), Clofazimine (Cfz), Prothionamide (Pto), Pyrazinamide (Z), Ethambutol (E) and Isoniazid (H^b) - these 7 drugs were taken together daily for an initial 4-month period (intensive phase), thereafter only oral Moxifloxacin, Clofazimine, Ethambutol and Pyrazinamide were taken for the remaining 16 months (continuation phase). Kanamycin was administered to patients with normal audiometry while patients with abnormal audiometry received Capreomycin.

All prospective participants were made aware of the entire study protocol and allowed to make decision to participate or otherwise out of their own volition. Study approval was obtained from the ethical committee of the hospital.

Thirty-eight (38) patients completed the study in each group making a total of 76 participants.

Pure tone audiometry was conducted using the using the Hughson-Westlake 'ascending method' in which tones were initially presented well above threshold, then decreased to a level of inaudibility in 10dB steps, and again increased in 5dB steps till the single hearing level at which a response was obtained three times was reached [8]. The pure tone threshold average was derived with figures at 500Hz, 1,000Hz, 2,000Hz and 4,000Hz frequencies.

The criterion for determining change in hearing was the ASHA 1994 criteria [8]. Data collected was analyzed with IBM Statistical Package for Social Sciences (IBM SPSS) version 20.0 software for Windows. Statistical significance was set at $p < 0.05$.

The entire study spanned 18 months (April 2019 to September 2020).

RESULTS

Table 1: Sociodemographic profile of study participants.

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

Table 2: Classification of hearing levels of test group participants.

Hearing Classification	AIR CONDUCTION						BONE CONDUCTION					
	RIGHT			LEFT			RIGHT			LEFT		
BASELINE	M	F	Total	M	F	Total	M	F	Total	M	F	Total
NORMAL	7	3	10(26.3)	7	3	10(26.3)	13	7	20(52.6)	11	8	19(50.0)
MILD	13	9	22(57.9)	11	10	21(55.3)	9	8	17(44.7)	11	7	18(47.4)
MODERATE	3	3	6(15.8)	5	2	7(18.4)	1	0	1(2.6)	1	0	1(2.6)
SEVERE	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
PROFOUND	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
FIRST MONTH												
NORMAL	3	2	5(13.2)	5	1	6(15.9)	12	4	16(42.1)	11	5	16(42.1)
MILD	14	7	21(55.3)	11	8	19(50.0)	8	7	15(39.5)	8	6	14(36.8)
MODERATE	6	5	11(28.9)	7	4	11(28.9)	3	3	6(15.8)	4	3	7(18.4)
SEVERE	0	0	0(0.0)	0	1	1(2.6)	0	1	1(2.6)	0	1	1(2.6)
PROFOUND	0	1	1(2.6)	0	1	1(2.6)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
SECOND MONTH												
NORMAL	4	1	5(13.2)	3	1	4(10.5)	9	4	13(34.2)	6	2	8(21.1)
MILD	9	6	15(39.5)	8	7	15(39.5)	9	4	13(34.2)	8	6	14(36.8)
MODERATE	9	5	14(36.8)	9	3	12(31.6)	4	5	9(23.7)	9	5	14(36.8)
SEVERE	1	2	3(7.9)	3	3	6(15.8)	1	2	3(7.9)	0	2	2(5.3)
PROFOUND	0	1	1(2.6)	0	1	1(2.6)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
THIRD MONTH												
NORMAL	2	2	4(10.5)	3	1	4(10.5)	7	2	9(23.7)	6	2	8(21.1)
MILD	9	3	12(31.6)	6	5	11(29.0)	6	6	12(31.6)	5	5	10(26.2)
MODERATE	6	5	11(29.0)	6	4	10(26.2)	9	4	13(34.2)	9	4	13(34.2)
SEVERE	5	3	8(21.0)	7	4	11(29.0)	1	3	4(10.5)	3	4	7(18.5)
PROFOUND	1	2	3(7.9)	1	1	2(5.3)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)

M = Male. F = Female

Table 3: Classification of hearing levels of control group participants.

Hearing Classification	AIR CONDUCTION						BONE CONDUCTION					
	RIGHT			LEFT			RIGHT			LEFT		
BASELINE	M	F	Total	M	F	Total	M	F	Total	M	F	Total
NORMAL	9	3	12(31.6)	8	3	11(28.9)	11	5	16(42.1)	13	5	18(47.4)
MILD	11	8	19(50.0)	11	9	20(52.6)	11	9	20(52.6)	9	10	19(50.0)
MODERATE	3	4	7(18.4)	4	3	7(18.4)	1	1	2(5.3)	1	0	1(2.6)
SEVERE	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
PROFOUND	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
FIRST MONTH												

NORMAL	9	3	12(31.60)	9	3	12(31.6)	11	5	16(42.1)	13	5	18(47.4)
MILD	10	8	18(47.4)	10	9	19(50.0)	11	9	20(52.6)	9	10	19(50.0)
MODERATE	4	4	8(21.1)	4	3	7(18.4)	1	1	2(5.3)	1	0	1(2.6)
SEVERE	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
PROFOUND	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
SECOND MONTH												
NORMAL	9	3	12(31.6)	9	2	11(28.9)	11	5	16(42.1)	11	5	16(42.1)
MILD	10	8	18(47.4)	10	10	20(52.6)	11	9	20(52.6)	11	10	21(55.3)
MODERATE	4	4	8(21.1)	4	3	7(18.4)	1	1	2(5.3)	1	0	1(2.6)
SEVERE	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
PROFOUND	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)
THIRD MONTH												
NORMAL	9	3	12(31.6)	8	1	9(23.7)	11	5	16(42.1)	11	5	16(42.1)
MILD	10	6	16(42.1)	11	11	22(57.9)	10	9	19(50.0)	10	10	20(52.6)
MODERATE	4	6	19(26.3)	4	3	7(18.4)	2	1	3(7.9)	2	0	2(5.3)
SEVERE	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
PROFOUND	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)	0	0	0(0.0)
TOTAL	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)	23	15	38(100.0)

M = Male. F = Female

Table 4: Prevalence of hearing impairments among the study participants.

	Drug resistant group			Control group		
	Normal (%)	Abnormal (%)	Total (%)	Normal (%)	Abnormal (%)	Total (%)
Baseline	10 (26.3)	28 (73.7)	38(100.0)	12 (31.6)	26 (68.4)	38 (100.0)
Cumulative incidence over 1 month		4 (10.5)			0 (0.0)	
First month	6 (15.8)	32 (84.2)	38 (100.0)	12 (31.6)	26 (68.4)	38 (100.0)
Cumulative incidence over 2 months		4 (10.5)			0 (0.0)	
Second month	6 (15.8)	32 (84.2)	38 (100.0)	12 (31.6)	26 (68.4)	38 (100.0)
Cumulative incidence over 3 months		6 (15.8)			0 (0.0)	
Third month	4 (10.5)	34 (89.5)	38 (100.0)	12 (31.6)	26 (68.4)	38 (100.0)

Table 5: Laterality of hearing among study participants.

	Drug Resistant			Control		
	Unilateral	Bilateral	Total	Unilateral	Bilateral	Total
BASELINE	4	24	28	5	15	20
THIRD MONTH	7	27	34	7	15	22

Table 6: Pattern of threshold shift among study participants.

	Drug Resistant			Control		
	Shift	No shift	Total	Shift	No shift	Total
BASELINE	-	38	38	-	38	38
THIRD MONTH	17	21	38	0	38	38

Table 7: Comparison of mean pure tone averages between study groups.

Study group		AIR CONDUCTION			BONE CONDUCTION		
		Means to compare	Mean PTA values	p-value	Means to compare	Mean PTA values	p-value
Drug resistant	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	
Control	Right	Baseline PTA	32.7±9.1	0.348	Baseline PTA	25.5±8.3	0.277
		Third month PTA	34.7±9.3		Third month PTA	27.5±8.4	
	Left	Baseline PTA	32.4±3.6	0.334	Baseline PTA	28.8±6.1	0.266
		Third month PTA	34.4±8.6		Third month PTA	29.9±7.8	

PTA = Pure tone average.

Table 8: Comparison of hearing levels between study groups.

	AIR CONDUCTION						BONE CONDUCTION					
	BASELINE			THIRD MONTH			BASELINE			THIRD MONTH		
	DR	C	p-value	DR	C	p-value	DR	C	p-value	DR	C	p-value
RIGHT												
NORMAL	10	12	0.743	4	12	0.002	20	16	0.629	9	16	<0.001
MILD	22	19		12	16		17	20		12	19	
MODERATE	6	7		11	10		1	2		13	3	
SEVERE	0	0		8	0		0	0		4	0	
PROFOUND	0	0		3	0		0	0		0	0	
LEFT												
NORMAL	10	11	0.893	4	9	0.001	19	18	0.989	8	16	<0.001
MILD	21	20		11	22		18	19		10	20	
MODERATE	7	7		10	7		1	1		13	2	
SEVERE	0	0		11	0		0	0		7	0	
PROFOUND	0	0		2	0		0	0		0	0	

DR = Drug-resistant group. C = Control group

DISCUSSION

Thirty-eight (38) patients treated for drug-resistant pulmonary tuberculosis completed the study alongside thirty-eight (38) control subjects (matched for age and sex) with a male-to-

female (M:F) ratio of 1.53:1. Majority of the patients (31.6%) were in the 41-50 years age bracket representing a significant proportion of people in their active years. Similar demography was described in a population-based study of 5,684 tuberculosis patients by Zhang et al[9]. We recorded a mean age of 48.3 ± 16.1 years which although higher, is comparable with mean ages recorded by similar researches by Sogebi et al (34.5 years)[10], Ramma and Ibekwe (33.0 years)[11], and Duggal et al (39.9 years)[12]. In this study, we found the pre-treatment (baseline) prevalence of hearing impairment to be 73.7% and 68.4% in the test and control groups respectively. These seemingly high prevalence were derived by considering participants with air conduction thresholds above 25dB in at least one ear as having some form of hearing impairment[13]. This did not necessarily translate to disabling hearing impairment as only 8 subjects (21.1%) in the test (drug-resistant) group and 3 (7.9%) from the control group self-reported hearing difficulty at the start of the study. By the third month of follow up, the prevalence of hearing impairment among the test group was 89.5% implying a cumulative impairment incidence of 15.8%. This difference was statistically significant ($p < 0.001$). The prevalence of hearing impairment among the control group remained unchanged after 3 months. Sogebi et al reported comparable prevalence of abnormal hearing (78.8%) among the 132 drug-resistant patients they studied, however their work did not study a control group for comparison[10]. In addition, follow up audiometry was conducted after 2 weeks of commencement of second line drugs for tuberculosis. Slightly lower prevalence (61%) was found by Ibekwe and Nwosu in Port Harcourt, Nigeria after 3 months of treatment with second line drugs with majority of their patients (94%) developing bilateral sensorineural hearing loss[14]. Although their sample size of 28 patients is comparable with our study's, there was no record of statistics for a control group[14]. They reported a higher cumulative incidence of 43.0% after 3 months[14]. In Brazil, Vasconcelos et al reported hearing impairment in 69.7% of patients treated for drug-resistant tuberculosis in a cross-sectional study that did not follow up the patients[15]. Since there was no baseline audiometry for comparison, it is impossible to relate their overall outcome with ours. Conversely, a relatively large study in Namibia by Sagwa and colleagues which assessed 353 patients on treatment for drug-resistant tuberculosis reported all the patients studied as having normal baseline hearing but recorded a cumulative hearing loss incidence of 58% at the end of intensive phase of treatment[16]. This proportion being lower than ours, may be due to the obviously larger size of their study having been conducted over 10 years and in 4 major treatment centres in Namibia. The lack of comparison with normal controls may be perceived as a drawback for the study in this context, even though arranging effective controls for such a large study spanning a decade would have been a herculean task. Appana et al in South Africa, followed up patients on treatment for drug-resistant tuberculosis for 5 months and reported a hearing loss prevalence of 52% by the first month and 100% by the fifth month of treatment[17]. This suggests that patients receiving prolonged administration of second line medications for tuberculosis have significant likelihood of developing hearing impairment. It is not exactly clear how much ototoxic medication can be projected to cause hearing loss among these patients as different studies report varying timelines for the onset of ototoxicity[10,18,19]. The cumulative incidence of hearing loss in our study was 10.5% each after the first and second months of treatment suggesting that it might take between 1 and 2 months for hearing impairment to set in in patients on treatment for drug-resistant tuberculosis. Peloquin and colleagues report median time of onset of hearing loss of 9 weeks[18]. We also report significant threshold shift among our test group patients following the ASHA criteria[8]. Seventeen participants (44.7%) met the criteria for threshold shift after 3 months, whereas no participant met the criteria from the

control group. This difference, being statistically significant underscores the enormity of hearing loss attributable to second line anti-tuberculosis drugs. Jain et al found similar threshold shifts in their study of patients on treatment for drug-resistant tuberculosis[20]. Majority of their patients had shifts at the higher frequencies which was bilateral in 85.7% of study participants. We found statistically significant difference between the configurations of baseline and third month audiograms among the test group but not the control group. The predominant configuration among the test (drug-resistant) group after 3 months of treatment was sloping/descending, whereas there was barely any change in the configurations of the control group over the 3 months of study. Ibekwe and Nwosu found similar pattern in their study with the predominant configuration after 3 months being the sloping/descending variety[14]. In contrast, Sogebi et al found more rising/ascending than sloping/descending configuration in their study. This disparity may be because the audiometry in their study was done within only 2 weeks of commencement of treatment. It is a possibility that a different finding may have been obtained if audiometry was repeated further down the treatment timeline. Notably, we observed difference in the pre-treatment (baseline) proportion of drug-resistant patients with sloping/descending configuration (21.1% on the right and 26.3% on the left) and by the third month of treatment (52.6% on the right and 50.0% on the left), underscoring an obvious worsening of hearing, predominantly at the higher frequencies.

CONCLUSION

Our study concludes that:

1. Treatment of drug-resistant tuberculosis with second line drugs can cause significant hearing impairment within the first three months of treatment.
2. Hearing impairment attributed to treatment with second line anti-tuberculosis medications appears to affect the higher audiometric frequencies more than the lower frequencies.

The authors declare no conflict of interest.

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