Original Article

Pure tone audiometric findings in patients on second-line treatment for multidrug-resistant tuberculosis

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Abstract

Background: The need for second-line antitubercular medication has been on the increase due to the emergence of multidrug-resistant strain tuberculosis (MDR-TB) in our environment.

Aim: This study was to assess the effect of second-line antitubercular medication on hearing in patients with MDR-TB.

Patients and Methods: This is a prospective study of all the patients admitted to the MDR-TB center of the University of Port Harcourt Teaching Hospital between January and May 2013. All patients had pure tone audiometry done before and 3 months after commencement of second-line antitubercular medications. The second-line regimen used includes kanamycin, levofloxacin, cycloserine, pyrazinamide, and pyridoxine.

Results: The study had a total of 28 patients. There were 14 males and 14 females. The age range was between 18 and 68 years. Different degrees of high-frequency sensorineural hearing loss (SNHL) were seen in 14 patients after 3 months' therapy. There were 13 bilateral and 1 unilateral hearing impairment, 2 patients had profound SNHL. However, a good number had involvement of the speech frequencies.

Conclusion: Second-line antitubercular medication appears to have a tremendous effect on hearing. This raises a public health issue since there is a growing increase in MDR-TB in our environment.

Keywords: Multidrug-resistant tuberculosis, pure tone audiometry, second-line antitubercular drugs, sensorineural hearing loss

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Introduction

Tuberculosis (TB) is one of the leading causes of mortality and morbidity worldwide.[1] It's management has become more complex due to the emergence of increased resistance to the commonly used anti-TB drugs. The emergence of resistance to drugs used to treat TB has become an obstacle to effective global TB control.[2] World Health Organization (WHO) estimates about 650,000 cases of multidrug-resistant TB (MDR-TB) globally.[3] Nigeria is one of the top MDR-TB high-burden countries in the world.[3] As at 2011, Nigeria has an estimated MDR-TB rate of 2.2% and 9.4% among new and re-treatment TB cases. She ranks 10th among the 22 high-burden TB countries in the world and are among the 4 African countries with the highest burden of drug-resistant TB (DR-TB).[3]

The treatment of DR-TB requires the use of second-line anti-TB medication as the powerful 1st line medications - isoniazid and

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rifampicin cannot be relied on for the treatment of TB due to resistance.[4,5]

Second-line drugs require long-term use (18–24 months)[6] and are frequently associated with very high rate of unacceptable adverse drug reaction needing frequent interruptions and change of regimen. Incomplete and inadequate treatment is the most important factor leading to the development of resistance as it relates to the length of treatment.[7] The longer time therefore that is required to treat MDR-TB results in an additional risk of poor adherence to treatment and thus of treatment failure.[8]

The second-line anti-TB regimen/medications include the combination of one of each of the following groups: Injectable aminoglycosides - kanamycin, amikacin, capreomycin; fluoroquinolones - ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin; old bacteriostatic second-line anti-TB agents - ethionamide, protionamide, cycloserine, para-aminosalicylic acid, thioacetazone; anti-TB agents with unclear efficacy-clofazimine, amoxicillin/clavulanate, linezolid, clarithromycin.[2]

These are commonly administered for about 2 years using daily injections. Many of the second-line drugs are toxic and have severe side effects.[4] It is this toxicity that is the main concern in long-term administration of these aminoglycosides.[9] Ototoxicity and nephrotoxicity are dose-related adverse effects of aminoglycosides.[9,10] Nephrotoxicity is generally reversible, but damage to the auditory and vestibular system is usually permanent.[11]

Aminoglycosides are toxic to the cochlea by selectively destroying the basal hair cells of the basilar membrane which is required for high-frequency hearing.[12] They can also destroy the hair cells of the vestibule.[13] These drugs react with transition metal ions to produce reactive oxygen species (free radicals) which in turn damages the cells through an oxidative process.[12] Thus, hearing loss in those treated with aminoglycoside usually starts with the high-frequency loss with later progression to frequencies more associated with speech communication as drug exposure is continued.[14] The risk of hearing loss increases with duration of exposure, high dosage, and high serum concentration of the drug.[11] The aminoglycosides are all similar in proficiency and kanamycin being cheaper than amikacin and capreomycin, is commonly used in the developing countries.[11]

Hearing loss can also be conductive in patients with MDR-TB as most of them may develop chronic otitis media that is not drug related but from the TB, HIV-AIDS in those having associated disease.

The WHO classified hearing loss as follows: Normal hearing - 0–25 dB, mild hearing loss - 26–40 dB, moderate loss: 41–55 dB, moderately severe: 56–70 dB, and severe: 71–90 dB, profound: >91 dB.

Audiometric assessment helps to identify ototoxicity in these patients early with resultant drug adjustments so as to reduce hearing loss and therefore possible incapacitation.[15]

Despite the increasing literature on MDR-TB over the last few decades, few studies worldwide have investigated hearing loss in patients being treated.

This study was conducted to assess the effect of second-line anti-TB medications on hearing in patients with MDR-TB.

Patients and Methods

This was a prospective study conducted at the MDR-TB center of the University of Port Harcourt Teaching Hospital between January and May 2013 on patients receiving the second-line anti-TB medication.

The study included all the patients with MDR-TB, who were admitted during the period.

They all had pure tone audiometry (PTA) before (baseline) and 3 months after commencement of second-line medications. This was done in a sound treated room using a conventional audiometer with frequencies between 125 and 8000Hz.

Consent was obtained from all the patients. The results were analyzed with IBM SPSS(statistical package for social sciences) version 20.

Types and dosage of the second-line medication used are as follows: Intramuscular kanamycin 750 mg daily; tablet levofloxacin 750 mg daily; tablet pyrazinamide 1250 mg daily; capsule cycloserine 250 mg 12 hourly. This was used for all the patients in the study.

Criteria (ASHA'S 1994)[16] used for determining ototoxicity threshold shift from the baseline audiogram were:

- >20 dB at any one test frequency;
- >10 dB at any two adjacent frequencies;
- loss of response at three consecutive frequencies where responses were previously obtained.

Air-bone gap for conductive hearing loss is ≥15 dB.

Results

The total number of patients with MDR-TB in the center during the study was 28 and all took part in the study.

There were 14 (50%) males and 14 (50%) females giving a ratio of 1:1.

They were between the ages of 18 and 68 years [Table 1]. Majority of the patients were in the age range 31–40 (39%), this is closely followed by age 21–30 and 51–60 (21%).

Twenty-three (82%) of patients had normal audiogram in the baseline PTA with 2 (7%) having sensorineural hearing loss [Table 2]. There were 3 (11%) with conductive hearing loss.

In the PTA done after 3 months drug therapy, there were 11 (39%) normal audiograms, 17 (61%) had various degrees of hearing loss, among which 10 had only high-frequency threshold shift, and 7 had a flat audiogram [Table 3].

The shift was bilateral in 16 (94%) cases and unilateral in 1 (6%) case [Table 4]. Among those with bone conduction threshold shift 2 had profound hearing loss while 7 (41.2%) had involvement of their speech frequencies in addition. The patients with baseline abnormal audiograms in the 3 months after audiogram were more affected, their hearing loss got worse.

Discussion

MDR-TB has become a serious threat to health globally.[17] The degree or level of affectation of hearing is dependent on the duration of exposure, dosage, and serum concentration of the medication. It is also known that long-term use of these drugs is required in the management of this disease (18–24 months) hence strict adherence to treatment is very critical to the outcome.[8,18]

Few studies have actually investigated the effect of second-line anti-TB medication on hearing in our environment.

In this study, 61% of the patients had their hearing affected however some researchers reported hearing loss prevalence ranging from 6% to 18%.[18,19] Studies done by Duggal and Sarkar,[14] de Jager and van Altena[9] and Sturdy *et al.*[20] recorded 23%, 15%, and 23% hearing loss, respectively. In a study in Namibia, a prevalence of 13–67% was noted[21] while in Turkey it was 15.4–33%.[22] The high prevalence from this study could be because it was clinically ascertained unlike in some of these studies that used patients' complaints of problem in communication as hearing loss. In India, a prevalence of 18.75% MDR-TB hearing loss on second-line drug treatment was found as well as frequencies 4000–8000 Hz being affected first in 6.25%.[14] In comparison 58.8% in this study had the high frequency affected first, however, 43% of the patients with hearing loss had an affectation of their speech frequencies, in addition, developing flat audiograms.

The study done by Duggal and Sarkar[14] also shows that 33% of patients with hearing affectation had flat audiogram involving both the higher and speech frequencies. It has also been noted that loss at 4000 Hz can affect communication when there is a background noise even though it is not a speech frequency.[23] This shows that there is high level of affectation of patient's speech and communication with use of second-line medications. Kanamycin despite its high ototoxic and nephrotoxic properties is still in use in our environment where cost consideration is a major factor in patient management[14] it is more toxic to the cochlear,[24] but is still in use commonly because it is cheaper than amikacin and capreomycin.

While we depended on dosage manipulations and in few cases changing the drugs completely to minimize toxicity, some researchers report mainly change of the drug as a means of decreasing toxicity.[19]

There was symmetrical affectation of hearing in patients with aminoglycoside medication as shown in this study where 93% had bilateral hearing involvement. As Shown in Table 5.This passage discusses the level of high frequency being affected first 58.8%. This is more than that of high and speech frequencies together.

Two patients had profound hearing loss and were recommended that they have an augmentation with hearing aids.

Table 1: Age distribution

Age range (years)	Number of patients	Percentage
10-20	1	4
21-30	6	21
31-40	11	39
41-50	3	11
51-60	6	21
61-70	1	4
Total	28	100

Table 2: Baseline pure tone audiometry

	Number of patients	Percentage
Normal	23	82
Sensorineural hearing loss	2	7
Conductive hearing loss	3	11

Table 3: Pure tone audiometric after 3 months therapy

	Number of patients	Percentage
Normal audiogram	11	39
Threshold shift	17	61

Table 4: Threshold shift

	Number of patients	Percentage
Bilateral	16	94
Unilateral	1	6

Table 5: Frequency involvement

	Number of patients	Percentage
High frequency only (>2 kHz)	10	58.8
Speech frequency only (0.5-2 kHz)	0	0
Both	7	41.2

Aminoglycoside ototoxicity has been known to progress even after discontinuation of the drug.[25] This study, on the other hand, is short-term, and the patients are discharged from the facility after the 3 months intensive therapy to their different local DOT centers in their states for continued outpatient management making follow up impossible.

In this study, there was only one patient with HIV co-existing, some studies have found high co-infection of HIV and TB. Therefore, in Nigeria, while some saw no link between the two,[26] some claim the TB in Nigeria is HIV-driven.[27] The HIV prevalence in Nigeria is 4.1% in the general population while prevalence among TB patients moved from 2.2% in 1991 to 25% in 2010.[28]

The study had a number of limitations. Facilities were not available for checking the serum levels of the medications, especially kanamycin which would have helped in the monitoring of the dosage of the medications in these patients.

These patients are admitted for 3 months which is the duration of the intensive therapy in the center and thereafter are discharged to their different DOT locations for continued outpatient care making follow-up very difficult.

The audiometer used in this study did not include the ultra-high frequency thresholds which are better for this monitoring but rarely available.

Conclusion

The effect on hearing from aminoglycoside in a patient receiving second-line anti-TB medication is a serious challenge owing to the growing prevalence of MDR-TB in our environment. Complete and adequate treatment will help prevent the development of resistance. Early identification of ototoxic hearing loss and the institution of drug dosage adjustment will help to minimize or prevent the effect on hearing.

Recommendations

Since the hearing loss affects the high frequencies 4000–8000 Hz first in these patients it can be used as a monitoring indicator for ototoxicity development so as to reduce permanent hearing loss in them.

Hearing assessment should not be left until there is a report of communication problems otherwise it will then be detected only when irreversible damage has occurred.

Serial audiograms can be used to monitor ototoxic hearing loss development in these patients.

Some reseachers have suggested individualized dosing of the drugs using peak concentrations in the serum and individual patient`s pharmacokinetics parameters.

We are recommending a reduction in the frequency of the kanamycin from daily to an alternate daily dosage which will help in reducing the serum concentration of kanamycin and the effect on hearing. Change to other aminoglycoside can also be done following early detection of toxicity. Patients should be on continuous monitoring of the hearing and if possible monitoring of the serum level of the aminoglycoside used.

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Conflicts of interest

There are no conflicts of interest.

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