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Clinical predictors of aminoglycoside-induced ototoxicity in drug-resistant Tuberculosis patients on intensive therapy

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ABSTRACT

Objective: The study objectives were to determine the incidence of aminoglycoside-induced ototoxicity in institutionalized patients on intensive phase of therapy for drug-resistant Tuberculosis (DR Tb) and also to assess clinical factors which could predict the ototoxicity.

Methods: The study was a prospective analytical study among consecutive DR Tb patients who were admitted for intensive phase of therapy (of 4 months) at the DR-Tb center over a 12-month period. Patients were diagnosed as DR Tb using the Gene Xpert machine to confirm Rifampicin resistance. All eligible 70 out of 87 consenting patients were consecutively recruited into the study. Patients had baseline (admission) and serial pure tone audiometries (PTAs) performed at 4 weekly intervals until discharge after 4 months of admission. Audiometric confirmation of aminoglycoside-induced ototoxicity was done by comparing serial with baseline PTA.

Results: Among the 70 patients the male:female ratio was 1.7:1. Nine patients (12.9%) were retroviral-positive, and 16 patients (22.9%) were confirmed to have ototoxicity by audiometric criteria. The duration of treatment when ototoxicity was detected in the patients ranged 4–17 (Mean ± SD; 9.4 ± 3.4) weeks. Ototoxicity was detected in the audiometric low frequency ranges in 7 (43.8%) and at the high frequencies in 4 (25.0%) of the patients. Univariate analyses of clinical parameters found that age, underlying diabetes mellitus, deranged baseline PTAv >25 dB HL, BMI on admission and retroviral status were significantly associated, while sex and previous drug regimen failure were not associated with ototoxicity. Multivariate adjusted logistic regression analyses, controlling for sex, revealed age (OR = 1.068, $p = 0.018$), BMI on admission (OR = 0.673, $p = 0.012$) and retroviral positivity (OR = 8.822, $p = 0.014$) of patients could significantly predict aminoglycoside-induced ototoxicity.

Conclusion: Incidence of aminoglycoside-induced ototoxicity in DR Tb patients was 22.9%. The clinical predictors for ototoxicity were age, BMI on admission, and co-existing retroviral infection in the patients. Clinicians should consider these factors in making choices of aminoglycosides to be used during intensive phase of treatment with second line anti-Tuberculous therapy.

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1. Introduction

Aminoglycosides have remained a major group of drugs in the treatment regimen of all forms of Tuberculosis. This was premixed on the efficacy, bactericidal action, hypoallergenic effects and relatively good safety margins of the drugs in this group in combating the infection [1]. The toxic (oto and nephrotoxicity) side-effects associated with its long-term use has been a major concern to all health care givers [2] and limits its usage. Reported incidences of ototoxicity vary widely, depending on subject groups, treatment parameters, assessment methods, and definitional criteria of hearing impairment. It is nevertheless known that continuous use of aminoglycoside medications for at least 6 weeks [3] predisposes to hearing impairment. Aminoglycoside ototoxicity may be initially overlooked as it may start after the end of drug treatment or develop only slowly thereafter [1], but it ultimately becomes an irreversible and permanent hearing impairment.

Hearing rehabilitative measures in patients who have developed ototoxicity include use of hearing aids, cochlear implants and assistive listening devices [4]. Efforts have also been made in preventing the development of ototoxicity by use of antioxidants. In clinical trials, the safety and otoprotective effect of N-acetylcysteine NAC when co-administered with aminoglycoside [3] has been documented. Animal experiment observed attenuation of streptomycin ototoxicity by tetramethylpyrazine in guinea pig cochlea [5]. In contrast, vitamin E did not confer a statistically significant protection against gentamicin ototoxicity [6]. Novel methods aimed at reducing the burden of aminoglycoside-induced ototoxicity include development of non-ototoxic aminoglycosides [7] and designer aminoglycosides [8]. These are, however, still largely in the experimental stage and have not been adapted into the clinical setting. It appears there is no viable alternative to use of aminoglycosides in treatment of Tuberculosis at present.

In drug-resistant Tuberculosis DR Tb, patients have developed resistance to the first line anti-Tb drug regimen notably rifampicin, necessitating deployment of second-line drugs including injectable aminoglycosides for a prolonged duration of time, with its attendant risk of ototoxicity. While genetic predisposition has been discovered as a risk factor for development of aminoglycoside-induced ototoxicity [9], it is not certain if there are other clinical factors that could predispose to or predict such ototoxicity.

This study aimed to determine the incidence of ototoxicity in institutionalized patients receiving injectable aminoglycosides as part of intensive therapy for DR Tb. It also assessed clinical factors which could predict ototoxicity in these patients. Knowledge of these predictors could assist in reducing incidence and possibly lessen the burden of this morbidity.

2. Patients and methods

The study was a prospective analytical study conducted among DR Tb patients who were admitted for intensive phase of therapy at the Drug resistant Tuberculosis center, domiciled at the Sacred Heart Hospital (Special) Lantoro, Abeokuta, Nigeria. The study was conducted among patients that were admitted between January 1 and December 31, 2015.

Patients were diagnosed as DR Tb using the Gene Xpert machine MTB/RIF® to confirm Rifampicin resistance. All the patients were duly informed about the necessity for admission for the intensive phase of treatment, the need for their co-operation in achieving a good and reasonable treatment outcome, and the required medications to be taken. The standard drug regime used was injection Kanamycin, oral Levofloxacin, Cycloserine, Pyrazinamide, and Prothionamide for a total period of 20 months comprising the first 8 months (intensive phase) and subsequent 12 months (continuation phase). Injection Kanamycin was administered only during the intensive phase. The drug dosage was based on World Health Organization (WHO) dose weight band guidelines for the programmatic management of DR-Tb [10]. Specifically for injection Kanamycin, patients with weight band of 30–33 kg had dose of 500 mg; those within 34–40 kg had 625 mg, with graduation up to weight band of >70 kg who had 100 mg.

Some of the side effects associated with aminoglycosides including ototoxicity and nephrotoxicity were explained, and the need for patients to report any symptoms related to these was emphasized. The necessity of serial monitoring of the patients and their investigations including Pure Tone Audiometry (PTA) to detect ototoxicity was also explained. This study and its implications were introduced to the patients and they all consented to participate. Ethics approval for the study was obtained from the Ethics committee of Sacred Heart Hospital.

The socio-demographic and clinical information of each patient were obtained at the time of admission. These included the age, sex, previous drug medications and failures, and retroviral status. Weight and height were measured with a Standiometer, and the body mass index (BMI) calculated and recorded on admission. On otoscopy, patients that were found to have simple lesions in the ears like wax impaction, debris or foreign bodies in the external auditory canals had them removed. One patient had a healed tympanic membrane perforation in one ear, while all the others had intact tympanic membranes. Patients also had baseline PTA performed using a calibrated diagnostic audiometer (Amplivox 240) in a quiet environment with ambient noise of <40 dB SPL, within 2 weeks on admission. Subsequent PTAs were performed at 4 weekly intervals until patients were discharged after 4 months of admission. Subsequent audiometries were compared with the baseline audiometry in order to detect aminoglycoside-induced ototoxicity.

Aminogycoside ototoxicity was defined according to the American Speech-Language Hearing Association (ASHA) criteria as >20 dB pure-tone threshold shift at one frequency, >10 dB shift at two consecutive test frequencies, or threshold response shifting to "no response" at three consecutive test frequencies [11].

Attention was focused on patients who had otologic and/or vestibular symptoms like hearing impairments, noise in the ears, and symptoms relating to difficulty in maintaining balance. In patients who were diagnosed with ototoxicity, the main otologic symptoms, duration at which patients had been on injectable aminoglycosides and the audiometric frequencies

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