

Vestibulo-otologic Events in Drug-resistant Tuberculosis Patients on Medications

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Authors' contributions

This work was carried out in collaboration between all authors. Author OAS designed the study, analysed the data and wrote the manuscript. Author TOA assisted in designing the study and in data analysis. Author BOA did initial assessment of the patients to confirm diagnosis and while author SMO handled the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aims to document the onset, types and factors associated with vestibulo-otologic (VO) events among patients on treatment for drug resistant Tuberculosis (DRTb).

Study Design: This is a prospective study of patients with drug resistant Tuberculosis who were admitted for the intensive phase of treatment with injectable medications.

Place and Duration of Study: The study was carried out at drug resistant Tuberculosis (DRTb) centre, Sacred Heart Hospital, Lantoro, Abeokuta, Nigeria between October 2013 and December 2014.

Methodology: Patients with complaints referable to VO effects of medications were recruited into the study. Clinical evaluation included the type, onset and duration of the vestibular or otologic

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events. Further information were retrieved from the patients case note records which included age, sex, retroviral status, weight on admission and height, from where the body mass index (BMI) was calculated. Data analyses were performed using SPSS version 20.

Results: A total of 121 patients comprising of 80 male and 41 female patients. Modal age group distribution for all patients was the group 21-40 years (72.7%), while the mean age \pm SD was 32.9 ± 13.7 years. The duration of treatment ranged from 12 to 20 weeks, mean \pm SD= 14 ± 3.4 weeks. VO events occurred in 40.5%, vestibular events alone were in 27.3% while otologic events alone occurred in 33.1%. The VO events were noticed between 6-19 weeks of treatment (mean \pm SD= 11.1 ± 4.7 weeks). Dizziness/imbalance were the most common vestibular while tinnitus was the most common otologic event. Among the patients with VO events, 13/46=28.3%, had repeat pure tone audiometry, and 7 (15.2%) met audiometric criteria for ototoxicity.

Conclusion: Vestibulo-otologic events were common among DRTb patients in Nigeria. The major complaints started around 11 weeks on medication. Factors associated with the VO events were female gender, being underweight and retroviral positive.

Keywords: Drug resistant tuberculosis; medications; side effects; ototoxicity; vestibular complaints.

1. INTRODUCTION

Two major factors are emerging as threats to control of tuberculosis worldwide; the first is development of resistance to major known and proven anti-tuberculosis (antiTb) medications. AntiTb drug resistance is defined as reduction in susceptibility of *Mycobacterium tuberculosis* to anti-tuberculous agents. There are concerns about development of drug resistant tuberculosis, with some developing resistance to both isoniazid and rifampicin (multidrug resistance, MDR) and others with resistance to additional drugs (extensively drug resistant XDR) [1]. Multidrug-resistant tuberculosis (MDR TB) is a significant threat to global health and it is estimated to account for nearly half a million new cases and over 200,000 deaths in the year 2013 [2].

DRTb follows the trend of primary pulmonary Tuberculosis (Tb) being more common in low-economic developing countries. In India, 15.0% of the patients with primary pulmonary Tb developed drug resistance [3], while among those with extra pulmonary Tb, 19% cases were multidrug resistant (MDR) [4]. Among foreign-born persons in the USA, 53% had Tb, 22% were from population born in sub-Saharan Africa and Southeast Asia [5]. Isoniazid resistance was as high as 20% among recent entrants from Vietnam and 18% for recent foreign entrants from Peru [5].

The second major factor threatening Tb control is side effects of antiTb medications. Minor adverse effects are quite common and they can be easily managed with symptomatic treatment. However some adverse effects can be life-threatening;

these include ototoxicity and nephrotoxicity due to aminoglycosides, cardiotoxicity due to fluoroquinolones, gastrointestinal toxicity due to ethionamide or para-aminosalicylic acid, and central nervous system toxicity due to cycloserine [6]. Ototoxicity is a result of disruption of functioning hair cells in the cochlea and in the vestibular apparatus which presents with referable symptoms like hearing loss, tinnitus, vertigo and vomiting.

Ototoxicity from aminoglycosides ultimately leads to permanent hearing impairment which is a major morbidity. Managing physicians are expected to have a thorough knowledge of adverse effects associated with the use of second-line anti-Tb drugs, and routinely monitor the occurrence of adverse drug reactions [6]. Ideally patients on anti Tb medications should have serial monitoring of serum concentration of aminoglycosides and also hearing thresholds over the duration of treatment. While this may be desirable, it is laborious and constitutes additional stress on both the patient and managing physician, and it may be rarely practicable in clinical settings. We hypothesized and pondered if vestibulo-otologic (VO) events could predict ototoxicity before permanent hearing threshold shift develops in the patients.

This study aims to document the onset, types and factors associated with VO events in patients on treatment for DRTb. Early detection of symptoms will stimulate actions of adjustment and amendment of medications as appropriate. This will indirectly enhance compliance to medication, reduce incidence of ototoxicity and improve the quality of life of the patients.

2. MATERIALS AND METHODS

This is a prospective study of patients with drug resistant Tuberculosis who were admitted for the intensive phase of treatment with injectable medications at the DRTb center at Sacred Heart Hospital, Lantoro, Abeokuta, Nigeria. The patients were on treatment at different times between October 2013 and December 2014. All the patients had baseline (admission) audiometries prior to commencement of medications. In the process of health education for the treatment, patients were informed about some of the common side effects of the second line antituberculous injectable aminoglycosides which they were receiving. Particular mention was made of vestibular and otologic symptoms and patients were encouraged to report any of such events that they observed to the nurses and other care-givers. The patients with the complaints were thereafter referred to the researchers, who evaluated the patients clinically and characterized the symptoms. Clinical evaluation included the type, onset and duration of the vestibular or otologic events. Some of the patients also had follow-up audiological evaluation (pure tone audiometry).

Further information were retrieved from the patients case note records which included age, sex, retroviral status, weight on admission and height, from where the body mass index (BMI) was calculated. Informed consent was taken from each of the patients while ethics approval for the study was obtained from institutional ethics committee of the hospital.

Excluded from the study were patients in the extremes of age i.e. children less than eighteen years (legal age of consent), and elderly patients (above sixty years of age to minimize effects of presbycusis which is common in this age-group and can present with similar otologic and vestibular symptoms). Patients who had previous histories of ear diseases like suppurative ear diseases or vestibular or otologic symptoms prior to the commencement of medications were also excluded. There were ten patients that confessed to have worked in noisy environment previously, but they had no clinical nor audiometric findings to suggest noise induced hearing loss and were thus not excluded.

The information was added to the data of the affected patients in the information sheet of all patients treated during the study period. For the purposes of this research, patients were

thereafter categorized as either having vestibulo-otologic (VO) events i.e. side effects of medications or not.

The socio-demographic characteristics, onset and types of vestibulo-otologic events were summarized in descriptive statistics as percentages and proportions for discrete (categorical) variables, and means and standard deviations for continuous variables. Factors associated with these symptoms were comparatively analysed between patients with and without symptoms using Chi-square test (for qualitative variables) and student's t-test (for quantitative variables). These are presented in tabular and graphical forms. Data analyses were performed using SPSS version 20 (Chicago, IL).

3. RESULTS

One hundred and twenty one patients met the inclusion criteria for the study comprising of 80 male and 41 female patients. The modal age group distribution for all patients was the age group 21-40 years, constituting 72.7%, while the mean age \pm SD was 32.9 ± 13.7 years. There was no significant difference in the age group distribution between the sexes. Significant differences occurred in the BMI and retroviral status between the sexes as detailed in Table 1.

Patients were on admission at the treatment centre for a period ranging from 12 to 20 weeks, mean \pm SD was 14 ± 3.4 weeks. Forty-six patients had any of the vestibulo-otologic events giving a crude prevalence of 38.0%, with vestibular events being $33/121 = 27.3\%$, otologic events $40/121 = 33.1\%$ among the DRTb patients. The vestibulo-otologic events were noticed between 6-19 weeks, of treatment (mean \pm SD = 11.1 ± 4.7 weeks). The distribution of the events is shown in Table 2. Dizziness/imbalance were the most common vestibular while tinnitus was the most common otologic event. Among the patients, 28 (60.9%) had combinations of both vestibular and otologic events as represented in Fig. 1. Among the patients with VO events, $13/46 = 28.3\%$, had repeat Pure Tone Audiometry (PTA), with 7 (15.2%) meeting audiometric criteria for ototoxicity.

Table 3 is a comparative analysis of the factors associated with the VO events. Sex, retroviral status and BMI of the patients on admission were significantly associated, while age was not associated with the VO events.

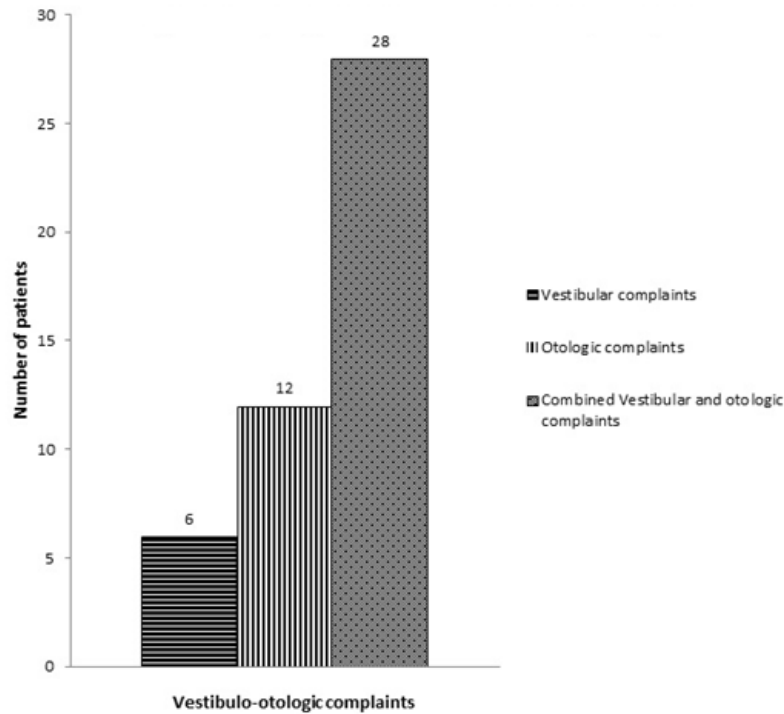


Fig. 1. Frequency distribution of vestibule-otologic complaints

Table 1. Socio-demographic characteristics of patients according to sex

Parameter	Male (n=80)	Female (n=41)	P-value
Age group (years)	%	%	
≤20	1 (1.3)	4 (9.8)	
21-40	58 (72.4)	30 (73.1)	
41-60	21 (26.3)	7 (17.1)	
Mean ±SD	32.9±13.7	29.2±13.3	.15
BMI (kg/m²)			
<18.5	29 (36.3)	28 (68.3)	
18.5-24.9	47 (58.7)	13 (31.7)	
25.0-29.9	4 (5.0)	- (0.0)	
Mean ± SD	19.7±2.7	17.4±2.6	< .001
Retroviral positive	9 (11.3)	10 (24.4)	.01

Table 2. Profile of vestibular and otologic events seen in 46 patients

Type	n	Percentage
Vestibular events		
Dizziness/imbalance	11	9.1
Vertigo	8	6.6
Light headedness	7	5.8
Neasea/vomiting	7	5.8
Otologic events		
Hearing loss	11	9.1
Tinnitus	23	19.0
Impaired sound localization	2	1.7
Impaired speech discrimination	4	3.3

Table 3. Factors associated with vestibulo-otologic events

Factor	Vestibulo-otologic events		Statistics	P-value
	Absent	Present		
Age (years)	35.0±10.5	34.3±9.7	0.206	.84
Sex (female)	19 (25.2%)	22 (47.8%)	6.439	.01
Retroviral positive	4 (5.3%)	15 (32.6%)	16.025	<.001
BMI (kg/m ²)	19.7±2.9	17.7±2.9	3.955	<.001

4. DISCUSSION

Major adverse drug reactions (ADRs) are common during anti-tuberculosis first and second line chemotherapy; in Republic of Korea, it was reported to occur in more than one in six (16.7%) of subjects with tuberculosis [7], while 61.5% of MDR Tb patients in Ireland developed ototoxicity from long-term use of aminoglycoside [8]. In the present study, 38.0% of the patients with DRTb had VO side effects of medications.

Aminoglycoside antibiotics are most notorious for being toxic, primarily targeting the renal and cochlea-vestibular systems [9]. Although the renal damage is reported to be generally reversible with cessation of treatment, both the cochlear and vestibular damage have tendencies to become non-reversible [10]. Some patients had combination of vestibular and otologic symptoms, whereas there were slightly more patients with otologic compared with those with vestibular events alone. Tinnitus was the most common of these symptoms, followed by hearing impairment, the combination of these can apparently be assumed as warning signs for ototoxicity, which is a major morbidity. Tinnitus and hearing impairment were also common complaints reported in a similar study conducted in South Africa [11].

The effects of aminoglycoside antibiotics on the hair cells is a non-reversible damage leading to hearing loss especially in the high frequencies [10]. Recent findings suggest that disruption of the actin cytoskeleton induced by kanamycin in cochlear sensory cells is mediated by Rac1 activation and the formation of superoxide by NADPH oxidase. Free radicals may in turn affect the RhoA/p140mDia gene pathway regulating actin, and affect cell survival and apoptotic pathways, ultimately resulting in loss of hair cells [12]. Furthermore, pre-existing hearing loss can increase the risk of toxicity of these antibiotics to the inner ear. The cumulative dose, duration of treatment and repeated courses of therapy are critical determinants of toxicity at the inner ear [13]. It is thus important to make enquiries from

patients about pre-existing hearing impairment, and previous antiTb drug regimen failure before commencement of second line medications.

Patients describe vestibular symptoms with different overlapping sensations including dizziness, vertigo, light-headedness and imbalance. Their causes are also varied and include malnutrition, hypotension and metabolic disorders which should be considered in the differential diagnosis. The most tasking vestibular event among these is vertigo which is a sensation of turning of the individual relative to the environment or vice-versa. However sensations of dizziness, imbalance or vertigo can all be disturbing, having the tendency to elicit fear with propensity to discontinue treatment in such patients. The development of side effects was one of the factors independently associated with default from treatment in DR Tb patients in Armenia [14]. In this study we found that the VO events started on the average, around the 11th week on medications. It is important to note that hearing problems due to ototoxic drugs may ensue from just a few minutes to several days after drug administration [15]. However, late and slowly progressive hearing loss occurring months or even years later has been reported to be possible. It is thus important to educate patients on such medications to report as early as they observe or experience any of the symptoms, while enquiries should still be made on these after patients have been discharged from the hospital, or even completed the anti Tb medications.

There is variation in both the choice of injectable agent and in ototoxicity screening practices at different treatment centres. In our centre, we usually start our patients on injectable kanamycin, to discontinue and substitute it with capreomycin if patients present with persistent VO symptoms. Capreomycin had been reported to be associated with less ototoxicity compared with kanamycin and amikacin, however long-term morbidity from capreomycin injectable treatment had been found even in well-resourced clinical settings [16]. There are other common ototoxic

drugs including non-steroidal anti-inflammatory drugs, antimalaris like chloroquine and quinine. None of the patients however gave an indication of prolonged use of any of these medications or any previous symptoms to suggest ototoxicity.

Recently there have been advances in the understanding of the genetic basis of drug-resistant tuberculosis. With the sequencing of the whole genome of *Mycobacterium tuberculosis*, the possibility of new targets for drug development has emerged [1]. Moreover, research is continuing on ways of ameliorating these side effects with focus on immune adjunct to chemotherapy. V-5 Immunitor was adjudged safe and effective as an immune adjunct to chemotherapy for Tb and can potentially reduce the treatment duration down to 1 month [17]. Regardless of these efforts, search for the ideal antiTb medication continues. Ideally PTA should be performed serially on all patients, and 15.2% of our patients had audiometric evidence of ototoxicity. However, in resource limited areas where such serial monitoring could not be performed, the VO events can be used as surrogates to assess likelihood of ototoxicity before permanent and irreversible changes occur.

There is the possibility that the VO symptoms were potentiated or cumulative events. This is premised on the fact that some of the patients had previous anti Tb drug failures during which time they also received injectable aminoglycoside therapy. Another possible stimulator is presence of noxious agents to which the ear had previously been exposed, especially noise. While the treatment centre environment was relatively quiet, some patients were in the habits of using head phones to listen to music with loud sound intensities that could not be regulated. There were ten patients who confessed to have previously worked in environments where they were exposed to loud and unregulated noise, although they did not notice any hearing loss prior to admission and commencement of second line antiTb therapy. Their admission (baseline) audiograms revealed subclinical levels of hearing threshold, especially the low tone hearing loss. Fausti et al. [18] explored effects between drugs and other noxious agents and reported that noise could act synergistically with aminoglycosides that have not fully cleared from the inner ear thereby increasing the patient's susceptibility to hearing loss for several months after completion of aminoglycoside therapy.

Ototoxicity from aminoglycosides is associated with high tone hearing loss especially at supra-high -frequencies above 8 kHz, which is not measured during conventional diagnostic pure tone audiometry. There are specific and stringent criteria in diagnosing ototoxicity from audiograms [19]. Thus audiological evaluation of patients should ideally be serial audiometric measures, including the ultra -high frequencies. Unfortunately only 13 out of the 46 patients (28.3%), had follow-up audiological assessments after VO events, with 7 (15.2%) fulfilling audiometric criteria for ototoxicity. Probably with further audiometric follow-up assessments, more patients will fulfill the audiometric criteria for ototoxicity. It is obvious that our management of these patients in this regard was substandard, and this finding will serve as an impetus for us to scale-up and improve our management efforts.

Vestibular disorders have generally been shown to be more common in females [20]. Hormonal fluctuations and derangements was one of the factors suspected to be responsible for this. In fact, data suggested that hormonal fluctuations (especially during menopause) may increase the tendency to develop vertigo [21]. The female sex was also reported as a predictor for longer sputum culture in Tb patients [22]. Another probable reason for the significantly more females having VO events in this study might be because a greater proportion of them were underweight. Lower weight has generally been associated with worse treatment outcomes in Tb. Compared with patients with normal weight (BMI ≥ 18.5 kg/m²), severely underweight patients (BMI < 16 kg/m²) had longer time to initial sputum conversion (adjusted hazard ratio, aHR 0.55, 95%CI 0.37-0.84) and a lower probability of sputum culture conversion within 4 months (adjusted relative risk 0.67, 95%CI 0.54-0.83) [22]. Similarly, baseline weight and degree of weight change during the first 6 months of treatment of Tb can help identify persons who are more likely to have poor outcomes and require other interventions [23]. While the low BMI found to be significantly associated with development of VO events is intriguing, we could not confirm a causal relationship as the study was not designed for this.

There are some limitations that were observed in this study. This includes the fact that all patients with the VO events should have had serial PTA, to confirm or refute ototoxicity. It would have been necessary to compare patients with and without previous anti Tb medication failure in the

development of the VO symptoms. Finally there was no adequate follow-up of the patients after discharge from the treatment centre, while the patients were receiving medications as out-patients. We hope to address these limitations and possibly control for them in our subsequent publications, since the study is continuous.

5. CONCLUSION

It will suffice to conclude that VO events are common among DRTb patients in Nigeria. The factors associated with the VO events were being a female, being underweight and retroviral positive. Due to poor coverage of audiometry in the affected patients (only 28.3%), the sensitivity of VO events as a predictor could not be conclusively demonstrated. However future studies, specifically designed to test this, may be more successful. In addition, lack of prolonged follow-up also limits the assessment of VO events sensitivity in this study. We intend to scale up our toxicity follow-up schedules to at least twelve months after completion of injectable aminoglycosides for early detection of progressive and delayed ototoxicity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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