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Ototoxicity in drug-resistant tuberculosis patients - a case report emphasizing the importance of audio-vestibular monitoring during treatment

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Abstract: *A case of profound hearing loss developing in a patient with previously normal hearing following drug treatment for drug-resistant tuberculosis is reported. At present there are no specific audio-vestibular monitoring recommendations in most drug-resistant tuberculosis programs, and patients are at a high risk of developing irreversible ototoxicity before it is discovered. The report emphasizes the need for frequent and regular monitoring of the audio-vestibular system during treatment for drug-resistant and multi-drug resistant tuberculosis, the need for policy support for such monitoring and the need to develop innovative solutions to the financial and logistical challenges that such policies and monitoring would create.*

Keywords: *Audio-vestibular monitoring, Drug-resistant tuberculosis, Hearing loss, Ototoxicity, Vestibular toxicity.*

I. Introduction

The treatment of drug-resistant tuberculosis (DR-TB) involves the use of multiple medications, and a wide range of adverse drug reactions and toxicity can occur during treatment [1, 2]. Although the response of an individual patient to the therapy cannot be predicted, adverse reactions and toxicity accompany essentially all treatment courses and categories (CAT I through CAT IV) [1]. While some patients will readily tolerate the medications, others may have serious problems. The adverse reactions that may occur include gastrointestinal reactions, mild to severe hypersensitivity reactions (including dermatologic) and haematologic abnormalities. Toxicity to the nervous system (central and peripheral), ototoxicity, ophthalmic toxicity, nephrotoxicity, musculoskeletal adverse effects are also common. Other miscellaneous adverse effects that can occur include gynaecomastia, hypothyroidism, hair loss and psychosis [1]. Despite these adverse effects and the difficulty with which some patients tolerate the anti-tuberculosis medications, the severity of DR-TB and the risk that it poses to public health strongly puts the risk-benefit analysis in favour of treatment with these medications, and the gold standard of care is that treatment should not be withheld because of fear of adverse reactions or complications of treatment [1, 2, 3, 4].

Ototoxicity in DR-TB management is a result of the aminoglycosides that are used as part of the combination therapy [1]. It is due to toxicity to the eighth cranial nerve and can manifest as vestibular or auditory toxicity or both [1, 2]. Unfortunately, while these complications are relatively common, not much attention is usually paid to them in the course of treatment of patients with DR-TB. This relative inattention is due to the complications not being perceived as directly life-threatening. While this may be so, it is important to note that ototoxicity, which may be irreversible[1], can result in severe impairment of the patient's quality of life with attendant anxiety and potential for progression to serious mental illness [1]. Also, ototoxic drugs are a major cause of hearing loss, which has been identified as the most prevalent cause of disability, affecting about 360 million people (5% of the world population) worldwide and concerted efforts are being made to control and reduce its prevalence[5, 6, 7]. If milder cases of hearing loss are included, almost 10% of the world population are affected by hearing loss [5, 6, 7].

This is a case report of a patient who developed profound hearing loss in both ears during the course of treatment for DR-TB. We present the case in order to emphasize the need to frequently and regularly monitor the auditory and vestibular functions of patients undergoing treatment for DR-TB and to respond promptly as soon as adverse effects are noticed. We also advocate that such monitoring should be made a policy issue in the management of patients with DR-TB so that these potentially devastating adverse reactions can be diagnosed early and adequate adjustments can be made to prevent or limit damage and disability, and provide adequate

psychological support for affected patients. Proper management of these patients is also necessary in order to ensure completion of their treatment and remove the risk that they pose to public health [2, 3].

II. Case Report

The patient was a 35 year-old housewife who was referred as a case of suspected tuberculosis to the chest clinic with a history of chronic cough that was productive of sputum, night sweats and weight loss. After assessment, she was found to have smear-positive tuberculosis which was diagnosed as Rifampicin resistant by the GeneXpert MTB/RIF diagnostic test. The result of a sputum culture received eight weeks later confirmed tuberculosis.

Immediately following diagnosis, the patient was educated about the disease and counseled with respect to the treatment side effects and the need to be compliant with treatment despite the possibility of side effects. The possible side effects were explained to her and she was assured that she would undergo regular monitoring available within the provision of the National Tuberculosis (TB) control program during the course of the treatment, and may need to have modifications of her treatment regimen as necessary especially if she experiences adverse effects. Having ensured that she understood the disease, the treatment schedule and possibility of complications during treatment, a documented voluntary informed consent was obtained from her to be treated for DR-TB treatment. In line with the World Health Organization/International Union Against Tuberculosis and Lung Disease recommendation and available local evidence (as recommended by the National TB control program), a plan was instituted to treat her with standardized second-line anti-TB medication for a minimum period of 20 months after completing a baseline work-up. The baseline parameters (including a check of HIV status and Pure Tone Audiometry – Figure 1) were satisfactory and she was commenced on an intensive phase of Kanamycin, Pyrazinamide, Levofloxacin, Cycloserine, Prothionamide and Pyridoxine to be delivered by Directly Observed Therapy (DOT).

She received her medications regularly and had converted to sputum-negative by the end of the third month of treatment. She also did not report any side effects until around the same time when she started complaining of difficulty in hearing in both ears. At this point, a Pure Tone Audiometry was conducted to assess her hearing (At her treatment center, until recently, when a consilium was inaugurated to ensure adequate clinical care for patients undergoing treatment for DR-TB, audiologic monitoring was only done for patients at the start of treatment, when patients complains of ear symptoms and at the end of treatment, as well as when indicated by the attending health officer). The Pure Tone Audiometry indicated that she had developed a high frequency sensorineural hearing loss in both ears, even though the Pure Tone Averages were still within normal limits in both ears (Figure 2). Kanamycin was however continued because of the fear of compromising her regimen and since there was no alternative available, with a plan to repeat audiometry monthly.

Pure Tone Audiometry at the end of the fourth month of medication (Figure 3) came back much worse than the previous one. Most of the frequencies were now affected in both ears and hearing loss in the left ear was profound while that in the right ear was bordering between severe and profound. At this stage a plan was made to switch to Capreomycin and an order was placed for it. Still, for fear of compromising her anti-TB regimen, Kanamycin was continued but with a view of changing her to Capreomycin as soon as it was available. A month later, Capreomycin was still not available and the patient was still on Kanamycin. The patient had now become inconsistent and had missed out seven days of medication during the month. Predictably, on audiometry the hearing loss was worse. She now had bilateral profound hearing loss.

Subsequently, she was fitted with hearing aids and counselled that she needed to continue with the treatment despite the hearing loss and reassured that the drug regimen would be reviewed to reduce chances of the hearing loss getting worse. Her husband was also counselled and taught to provide support for her. But despite all these measures, she continued missing treatment and eventually stopped showing up. Home visits were conducted but she refused to take the medications despite several attempts. She was also encouraged to continue to show up for hearing assessment and speech therapy but she has also stopped attending. Her last visit for audiometry was six months after she had started the anti-TB drugs and hearing loss remained profound bilaterally in both ears (Figure 4). However, efforts are still ongoing to convince her to return to treatment.

III. Discussion

The treatment of tuberculosis has come a long way since the days of Hippocrates (460-370 BC) when the concept of tuberculosis or consumption was established [8]. Many remedies were tried without significant success and until the 1940s the only remedies that seemed to have some effect were surgically collapsing the lung and sanatoriums [9]. The turning point came with the discovery of the first aminoglycoside, streptomycin in 1943 [10]. Its use, first as a single agent was limited by problems of resistance, but when it was later used in combination with Isoniazid, successful chemotherapy for tuberculosis was finally achieved [10]. The breakthrough laid the foundation for the present-day chemotherapy treatment for tuberculosis.

Better results followed the development of PAS (para-aminosalicyclic acid), INH (isoniazid) and RIF (rifampicin) and with the advent of these more effective anti TB medicines streptomycin was replaced in the initial treatment of TB [10]. However, with the resurfacing of tuberculosis as a public health problem and the emergence of multi-drug resistant tuberculosis there has arisen the need to use second line drugs in the chemotherapy of Multi-drug resistant tuberculosis MDR-TB [2, 11]. Depending on the individual susceptibility pattern, residual first-line oral drugs must are appropriately combined with additional second line drugs comprising injectable aminoglycosides (amikacin, kanamycin, capreomycin), fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin), old bacteriostatic second line anti-tuberculosis agents (ethionamide, protionamide, cycloserine, para-amino salicylic acid, thiocetazone) and anti-tuberculosis agents with unclear efficacy (clofazimine, amoxicillin/clavuanate, clarithromycin, linezolid) [2, 11].

Ototoxicity and nephrotoxicity are well recognized as dose-related adverse effects of aminoglycosides and have been of major concern because of the narrow therapeutic range of these agents and prolonged therapy in the management of tuberculosis [11, 12]. While there are specific protocols for monitoring nephrotoxicity [2], there is none for ototoxicity in aminoglycoside-treated MDR-TB patients in most TB control programs and guidelines. Most experts recommend weekly to fortnightly audiograms following the baseline evaluation [1] but financial and logistical barriers, and the absence of major policy support has undermined such frequent monitoring. It is more usual to see monthly assessments being done as was the case with the patient being reported. In most places actually, there is no monitoring until the patient complains of hearing symptoms.

The case here reported showcases an undesirable possible consequence of inadequate monitoring of side effects in the management of DR-TB and failure to institute prompt adjustments in treatment when necessary. The patient started treatment with normal hearing (Pure Tone Audiometry thresholds of less than 25dB [13]) in both ears and ends up six months later with bilateral profound hearing loss (Pure tone average of greater than 80 dB [13]). Not only is her hearing severely impaired, she has defaulted from treatment thereby putting her health in danger and remaining a high risk to Public Health. It is possible that more frequent monitoring and prompt decisive action to adjust treatment may have made the outcome better. The obvious drawback of an inadequate monitoring policy is that by that time hearing loss is discovered, the damage may already be done and it may be irreversible, even progressive. This is an unfortunate, though not unexpected situation as there are no specific recommendations for audio-vestibular monitoring either in the National protocol or in the most TB control program guidelines. Neither are there specific clearly spelt out actions to be taken when audio-vestibular toxicity is encountered. Consequently there are usually no programmatic provisions for frequent and regular monitoring within the usually-resource-constrained framework of most DR-TB control programmes at the implementation levels.

As demonstrated in this case, aminoglycoside induced hearing loss usually starts in the high frequencies and then slowly progresses to involve the lower frequencies [1]. Unfortunately most patients may not even complain of hearing loss until it becomes disabling. Hearing loss is said to be disabling in an adult when the hearing threshold in the better ear is 40dB or higher [13]. The goal of monitoring would be facilitate early detection, prompt reaction and rehabilitation but this can only be achieved with a strong monitoring policy. A strong policy would provide the opportunity to make adjustments to medication in order to give a chance to reverse or limit damage, and to get the patient psychologically prepared to handle any hearing loss if such eventually does occur. To fail to monitor adequately clearly increases the risk of ending up with a poorly prepared irreversibly disabled patient.

The same is the case with vestibular monitoring which is even less frequently done than auditory monitoring. In this patient there was no vestibular monitoring. Like auditory damage, vestibular damage is insidious. The onset of fullness in the ears and tinnitus may signify vestibular damage [1] and when a patient on aminoglycosides complains of tinnitus it should be taken seriously, thorough vestibular assessment done and attempts should be made to adjust therapy to reduce further damage if thought to be due to an aminoglycoside. Better still, baseline and regular vestibular assessments should be done and adjustments made at the earliest sign of vestibular dysfunction. Vestibular toxicity can cause irreversible severe vertigo and imbalance with consequent mental disability. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitates discontinuation of a class of agents [1].

Frequent and regular audio-vestibular monitoring will increase the costs of care and need for specialized personnel for DR-TB patient care. This may not seem practicable in developing countries because of limited funds for TB control programs. While it definitely creates a challenge, it does not obviate the need for the strict monitoring because it is in these resource constrained environments that the need for monitoring is more. For example, the patient presented in this report was on Kanamycin which is known to be more toxic to the cochlea than the other usually-used drugs. The cost of Kanamycin is one fourth the cost of Amikacin and one tenth the cost of Capreomycin [11].

The situation clearly calls for innovative solutions to help maintain monitoring in spite of the costs. First, there needs to be more advocacy for governments and multinational health agencies and TB control

programs to include specific recommended protocols for the monitoring of audio-vestibular toxicity in their guidelines. The funding of TB programs at governmental and non-governmental levels also need to be improved so as to facilitate monitoring of the toxicity of the drugs, and improved access to the highly specialized professionals that are needed. Finally, at the implementation levels, expert committees that oversee the care and monitoring of the patients should be strengthened and the patients themselves encouraged to partner with the programmes and caregivers, and if possible bear some or all of the costs of their monitoring where the programmes cannot fully pay.

IV. Figures

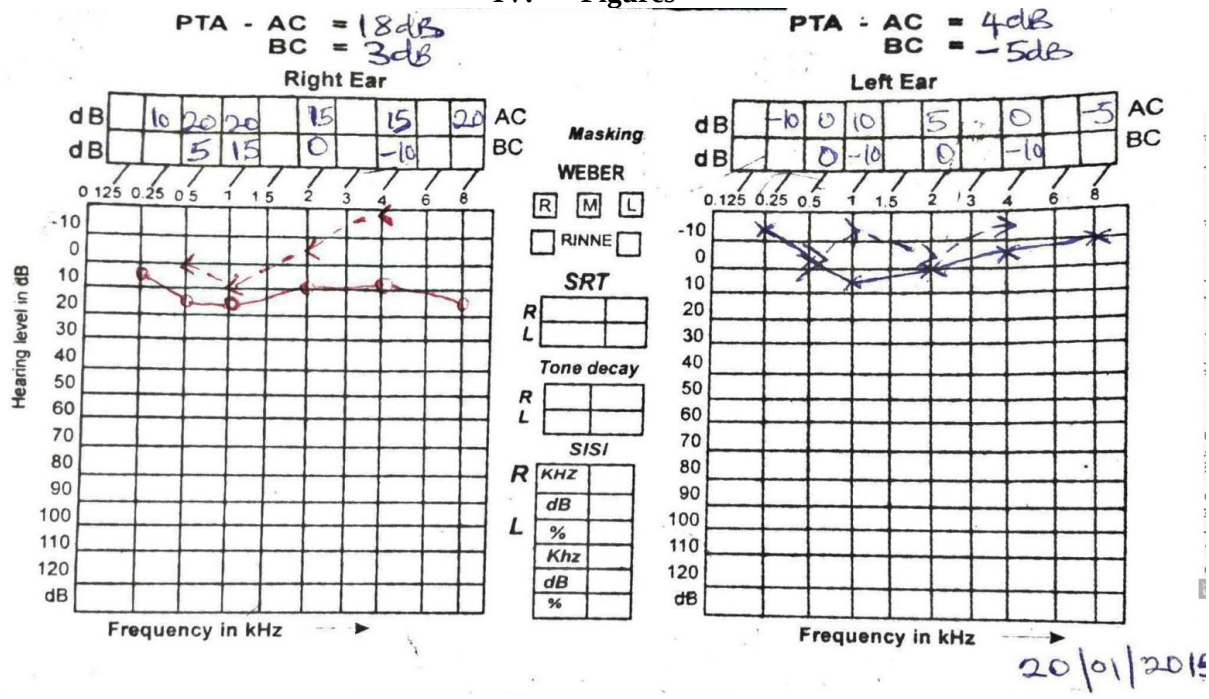

Figure 1: Baseline Audiogram (20/01/2015)

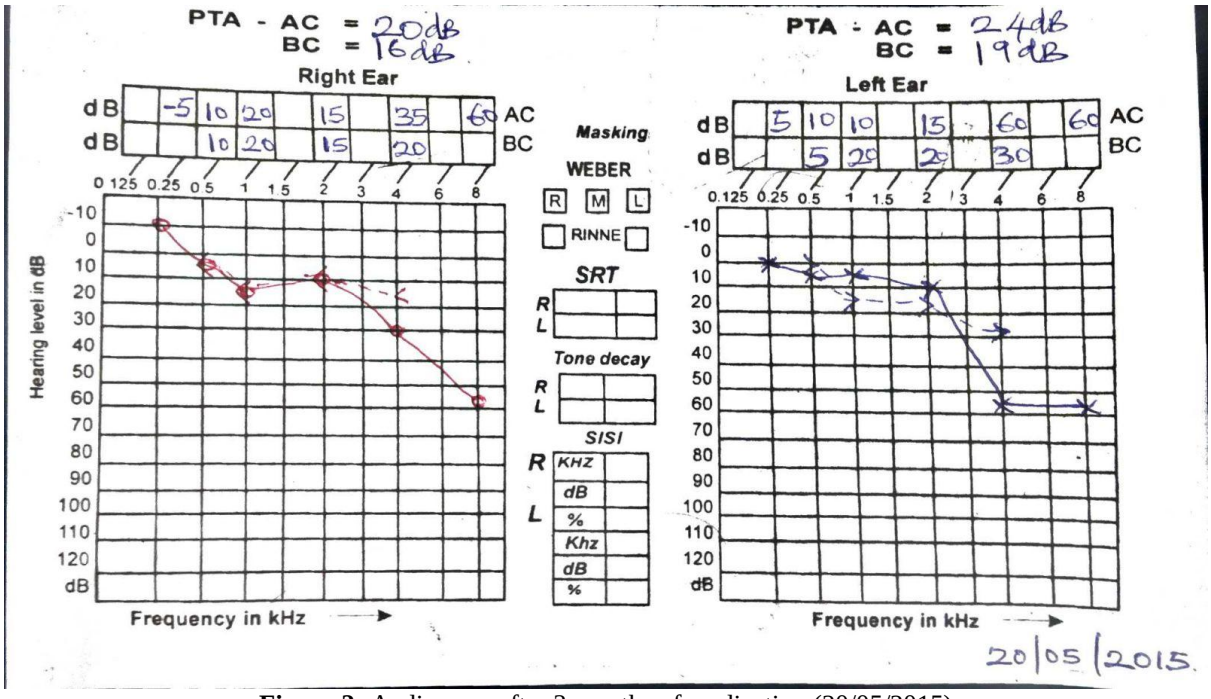

Figure 2: Audiogram after 3 months of medication (20/05/2015)

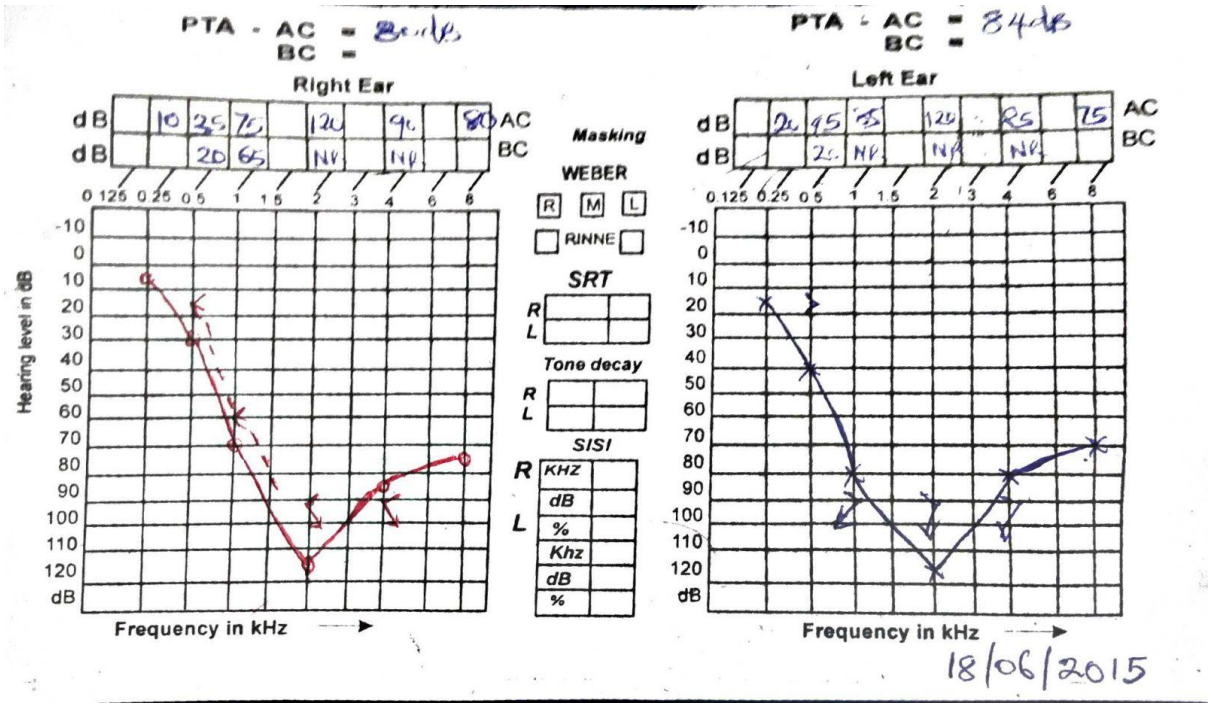

Figure 3: Audiogram after 4 months of medication (18/06/2015)

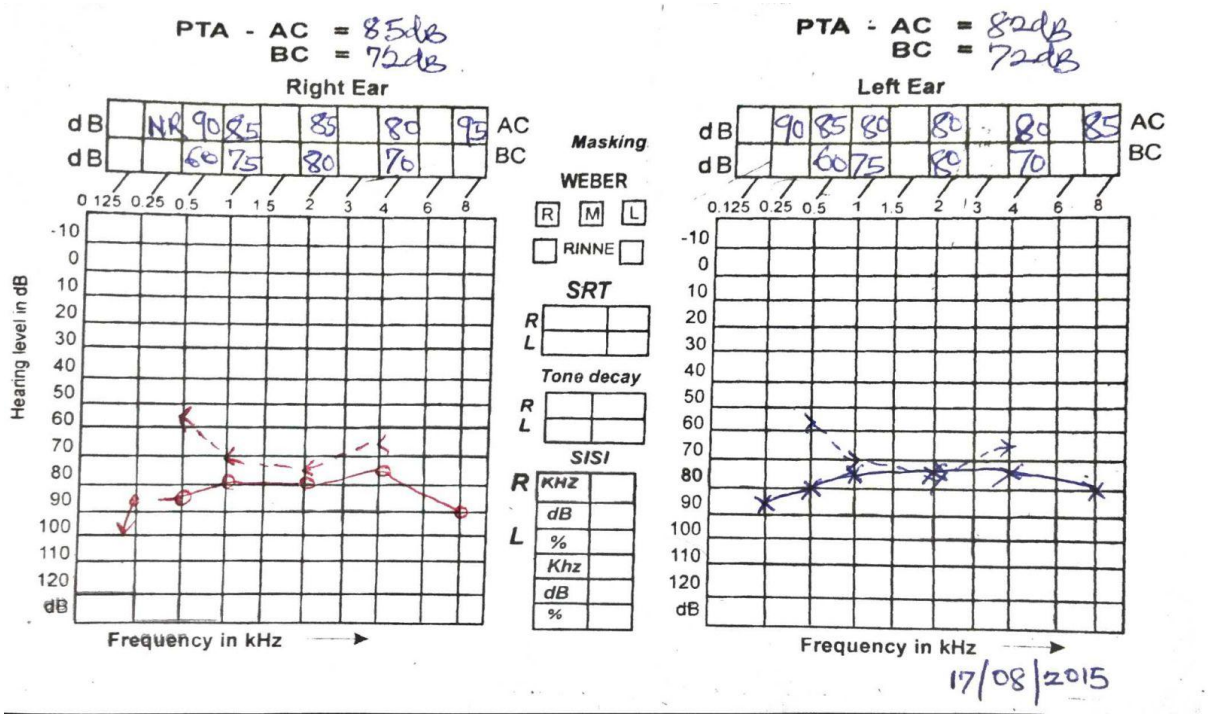

Figure 4: Audiogram 6 months after medications were commenced

V. Conclusion

The case reported here emphasizes the dangers of inadequate audio-vestibular monitoring of patients on medication for drug-resistant tuberculosis and of the weakness of policies concerning audio-vestibular monitoring for these patients. While ototoxicity may not seem immediately life-threatening, it can cause irreversible severe disability and pose a threat to mental health. Regular monitoring of the audio-vestibular system during treatment for drug-resistant and multi-drug resistant tuberculosis is important, as is the need for policy support for monitoring and for developing innovative solutions to financial and logistical challenges that such policies and monitoring would create.

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