Title: Audiological evaluation of multi-drug resistant tuberculosis patients: a retrospective study

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Abstract:

Background: Multi-drug resistant tuberculosis has emerged as a significant problem with the resurfacing of tuberculosis and thus the need to use the second line drugs with the resultant increased incidence of adverse effects. We discuss the effect of injectable second line anti-tubercular drugs on the hearing status of MDR-TB patients.

Study design: A retrospective study was undertaken

Methods: Sixty four patients were put on injectable second line anti-TB drugs. These were divided into three groups: group I, 34 patients using amikacin, group II, 26 patients using kanamycin and group III, 4 patients using capreomycin.

Results: 18.75 % of the patients developed sensory neural hearing loss involving higher frequencies while 6.25 % had involvement of speech frequencies also.

Conclusions: Injectable second line drugs used in MDR-TB patients result in development of irreversible hearing loss involving higher frequencies and can become a hearing handicap as speech frequencies are also involved in some of the patients thus underlining the need for regular audiological evaluation in patients of MDR-TB during the treatment.
Background: Tuberculosis is one of the leading infectious diseases in the world and is responsible for more than two million deaths and eight million new cases annually [1]. Emergence of resistance to drugs used to treat tuberculosis and particularly multidrug resistant (MDR-TB) has become an obstacle to effective global TB control [2]. Incomplete and inadequate treatment is the most important factor leading to its development, suggesting that it is often a man-made problem [3]. Inappropriate treatment results in unacceptably low cure rates and the continued spread of tuberculosis in the community because of selection of M. tuberculosis isolates that are resistant to anti tubercular drugs [4]. Taking into consideration the high success rate of TB treatment under DOT policy (Directly Observed Treatment), the principal cause for the generation of drug resistant TB generally appears to lie in the low degree of patient compliance with treatment [5]. Most of the problems from which drug-resistance originates are related to the length of treatment (especially considering tolerability and adherence), the longer time that is required to treat MDR-TB results in an additional risk of poor treatment adherence and thus of treatment failure [6]. Two other major issues of importance which affect the outcome in MDR-TB compared to drug-susceptible disease are the increased cost (up to 100 times higher) and the higher toxicity [7,8].

By definition, chemotherapy of MDR-TB cannot rely upon isoniazid and rifampicin, the two most powerful drugs for the treatment of tuberculosis [9]. Thus, depending on the individual susceptibility pattern, residual first-line oral drugs must be appropriately combined with additional second line drugs comprising of injectables (streptomycin, kanamycin, amikacin, capreomycin), flouroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin), old bacteriostatic second line anti-
tuberculosis agents (ethionamide, prothionamide, cycloserine, PAS, thioacetazine) and anti-tuberculosis agents with unclear efficacy (clofazimine, amoxicillin/clavulanate, clarithromycin linezolid) [2].

A crucial issue related to long-term administration of injectable group is toxicity. Ototoxicity and nephrotoxicity are well recognized as dose-related adverse effects of aminoglycosides. The toxicity profile of capreomycin is similar to that of aminoglycosides [10]. The present study was conducted to study the effect of injectable drugs (amikacin, kanamycin and capreomycin) on the hearing status in patients of MDR-TB after long term use as a part of multi-drug therapy.

Material and methods:

A total of 64 patients were included in the study who completed treatment for MDR-TB from April 2000 to September 2006 using second line drugs. Treatment regimens followed were based on drug susceptibility testing and previous treatment history. All the relevant data was recorded on MDR-TB patient sheets including the base line and follow-up investigations. Base line pure tone audiograms between 125 Hz and 8000 Hz were performed for all the patients in a sound proof room before the start of the treatment followed by audiograms every two month till completion of treatment. The patients complaining of hearing loss prior to start of second line drugs were excluded from the study. These patients were divided into three groups depending upon the ototoxic injectable drug used. Group I patients received amikacin, group II patients received kanamycin and group III patients received capreomycin as a part of complete regimen comprising of one injectable, one quinolone with a minimum of five drugs. Those patients receiving two ototoxic drugs were excluded from the study. Total
duration of therapy in all the patients ranged from 18 to 24 months after sputum smear/culture conversion and injectable ototoxic agent was used for six months after sputum conversion. Ototoxic injectable drug was stopped in patients complaining of or showing audiological evidence of hearing loss and substituted with other second line drug depending upon the drug sensitivity testing. The data so obtained was analyzed for various epidemiological factors and hearing status in each group after completion of therapy.

Results:

All the patients in this study were in the age group of 17 to 65 years (mean age of 39.9 years) with males constituting 60.9 % and females constituting 39.1 % (n=64). Majority of the patients were from rural background (68.7 %) while 31.2 % were from urban areas (n=64). Majority (65.6 %) of the patients were from low socio-economic status (n=64). 34 patients were put on amikacin (Group I), 26 on Kanamycin (Group II) while four patients were put on Capreomycin (Group III) along with other drugs depending upon the drug sensitivity testing and cost factors involved. The average duration of therapy was 18-24 months after smear/culture conversion while injectables were continued for 6 months (180 days) post conversion in the initial phase (average duration was 242.9 days). Seven patients (20.6%, n=34) of group I (amikacin) showed sensori-neural hearing loss (SNHL) involving the higher frequencies (4000-8000Hz). Amikacin was stopped on the first report of hearing loss and patient shifted to another of the second line drug. Follow-up audiogram showed in two (5.9 %, n=34) of these patients involvement of speech frequencies (500,1000 and 2000Hz) in one patient (Sr. No. 2) at six months and another (Sr. No. 4) after completion of injectable therapy. Four patients
of group II (kanamycin) had SNHL involving higher frequencies. In two (8.3\%, n=24) patients lower frequencies were also involved even when Sr. No. 8 had injectable drug stopped at 4 months while Sr. No. 10 had the drug stopped on report of high frequency loss at 6 months. One of the patients of group III (25.0\%, n=4) developed sensori-neural hearing loss involving high frequencies (Table 1). Overall incidence of hearing loss on audiogram was 18.75\% and the average duration after which loss developed was 160 days with 6.25\% patients having involvement of speech frequencies also (n=64). Average duration of treatment after which hearing loss was reported on pure tone audiogram was 162.8 days in group I, 165 days in group II and 120 days in group III (one of the four patients had hearing loss). None of the patients had any recovery in audiogram after stopping the injectable treatment.

Discussion:

MDR-TB is a growing problem throughout the world [11]. The selection of drug resistant M. tuberculosis depends on the frequency of the specific drug-resistant mutants in the initially drug-susceptible bacterial population. As a consequence, the chance of selecting such mutants is highest in the case of mono-therapy [4] and this is the rationale of combination chemotherapy both in case of drug-susceptible as well as MDR-TB even at the cost of adverse drug reactions so that mutants resistant to a single drug are not fairly easily selected by mono-therapy. Adherence to treatment is a critical factor in the management of MDR-TB and adverse events associated with second line drugs could have a severe impact on adherence as long term use of second line drugs is required in MDR-TB ranging from 18-24 months [12]. There exists a large literature on adverse effects of anti-tuberculosis medications, which range from minor to life threatening [11].
The present study evaluated the effect of parenteral second line drugs on hearing status of MDR-TB patients. We report a hearing loss documented by pure tone audiometry in 18.75% patients of MDR-TB using a single parenteral second line drug involving higher frequencies (4000 and 8000Hz) to start with and progressing to involve lower frequencies (500 Hz, 1000 Hz and 2000 Hz) in 6.25 % thus affecting the speech comprehension of the patient (n=64). The loss once developed was found to be irreversible and none of the patients in the present study showed any improvement on stopping the therapy. Persistence of toxicity of sera has been reported up to one year in patients using aminoglycosides even after stopping the ototoxic drug [13]. Different studies have reported hearing loss as an adverse drug reaction in patients of MDR-TB ranging from 6-18 % [11,12,14]. The finding that higher frequencies are involved before the lower frequencies may be used as a monitoring procedure for the detection of ototoxicity has the potential for preventing or minimizing irreversible communication deficits in patients receiving aminoglycoside therapy [15]. In all the patients showing hearing loss, the ototoxic drug was stopped and switch over to another second line drug was done. All the patients included in the present study completed the remaining part of the therapy. Other authors have also reported switching over to other second line drugs and completion of full therapy [11,12]. First row outer hair cells (OHCs) in the basal turn tend to be affected earlier than inner apical cells and type I cells are affected before type II cells. The progression of hair cell loss in cochlea tends to be from basal to apical and from OHCs to inner hair cells (IHCs) to supporting cells to more central neural structures like spiral ganglion cells [16]. This stepwise progression of damage explains the clinical findings of high frequency hearing loss occurring first with ototoxic drugs.
Conclusions:

Audiological changes have been reported in patients of MDR-TB using second line injectable drugs which can potentially affect the communication ability of the patient. But careful audiological monitoring can prevent this damage which once developed is permanent. Thus otologists can have an important role in the management of MDR-TB in preventing the treatment related morbidity.
Competing interests: None
Authors contributions:

DP participated in the study design, carried out audiological work and helped in drafting the manuscript. SM conceived of the study, outlined and carried out the management of the patients under study. Both the authors have read and approved the final manuscript.
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References:


Table I: Grouping of patients with duration of ototoxic drug use (in days*) and the audiogram findings.

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Drug used (Group)</th>
<th>Days*</th>
<th>PTA 0&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PTA 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PTA 4&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PTA 6&lt;sup&gt;d&lt;/sup&gt;</th>
<th>PTA 8&lt;sup&gt;e&lt;/sup&gt;</th>
<th>PTA C&lt;sup&gt;f&lt;/sup&gt;</th>
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<tr>
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<td>Amikacin (I)</td>
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<td>HFL</td>
<td>HFL</td>
<td>HFL</td>
</tr>
<tr>
<td>2</td>
<td>Amikacin (I)</td>
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<td>N</td>
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<td>HFL</td>
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<td>FLAT</td>
<td>FLAT</td>
</tr>
<tr>
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<td>HFL</td>
<td>HFL</td>
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<tr>
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<td>N</td>
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<td>HFL</td>
<td>FLAT</td>
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<tr>
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<td>N</td>
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<td>HFL</td>
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<td>N</td>
<td>HFL</td>
<td>HFL</td>
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<tr>
<td>8</td>
<td>Kanamycin (II)</td>
<td>120</td>
<td>N</td>
<td>N</td>
<td>HFL</td>
<td>HFL</td>
<td>FLAT</td>
<td>FLAT</td>
</tr>
<tr>
<td>9</td>
<td>Kanamycin (II)</td>
<td>180</td>
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<td>N</td>
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<td>HFL</td>
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<td>HFL</td>
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<tr>
<td>12</td>
<td>Capreomycin (III)</td>
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<td>N</td>
<td>HFL</td>
<td>HFL</td>
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<sup>a</sup>PTA 0 = Baseline pure tone audiogram,  
<sup>b</sup>PTA 2 = Pure tone audiogram after 2 months,  
<sup>c</sup>PTA 4 = Pure tone audiogram after 4 months,  
<sup>d</sup>PTA 6 = Pure tone audiogram after 6 months,  
<sup>e</sup>PTA 8 = Pure tone audiogram after 8 months  
<sup>f</sup>PTA C = Pure tone audiogram after completion of MDR-TB therapy,  
N = Normal, HFL = High frequency loss, FLAT = loss from 500Hz to 8000Hz.