Journal of Infection (2013) **66**, 320–329

BIAM British Infection Association

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Hearing loss in children treated for multidrug-resistant tuberculosis

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Accepted 2 September 2012
Available online 6 September 2012

KEYWORDS
Hearing;
Audiology;
Tuberculosis;
Multidrug-resistant;
Resistant;
Ototoxicity;
Children;
Paediatric

Summary *Objective:* The aminoglycosides and polypeptides are vital drugs for the management of multidrug-resistant (MDR) tuberculosis (TB). Both classes of drug cause hearing loss. We aimed to determine the extent of hearing loss in children treated for MDR-TB.
Methods: In this retrospective study, children (<15 years) admitted to Brooklyn Chest Hospital, Cape Town, South Africa, from January 2009 until December 2010, were included if treated for MDR-TB with injectable drugs. Hearing was assessed and classified using audiometry and otoacoustic emissions.
Results: Ninety-four children were included (median age: 43 months). Of 93 tested, 28 (30%) were HIV-infected. Twenty-three (24%) children had hearing loss. Culture-confirmed, as opposed to presumed, diagnosis of TB was a risk factor for hearing loss (OR: 4.12; 95% CI: 1.13–15.0; $p = 0.02$). Seven of 11 (64%) children classified as having hearing loss using audiometry had progression of hearing loss after finishing the injectable drug.
Conclusions: Hearing loss is common in children treated for MDR-TB. Alternative drugs are required for the treatment of paediatric MDR-TB.

Abbreviations: MDR, multidrug-resistant; DR, drug-resistant; TB, tuberculosis; WHO, World Health Organization; PTA, pure tone audiometry; OAE, otoacoustic emission; DPOAE, distortion product otoacoustic emission; BCH, Brooklyn Chest Hospital; IM, intramuscular; ASHA, American Speech and Hearing Association; OR, odds ratio; CI, confidence intervals; IQR, inter-quartile range.

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0163-4453/$36
http://dx.doi.org/10.1016/j.jinf.2012.09.002

Introduction

Multidrug-resistant (MDR) tuberculosis (TB) is an evolving global challenge with the World Health Organization (WHO) estimating there to be over 650,000 prevalent cases of MDR-TB in 2010.[1] MDR-TB is caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin.[2] As paediatric TB constitutes 15—20% of all TB cases in high burden settings,[3,4] a large number of children are likely to be affected by MDR-TB. Due to the paucibacillary nature of the pathology, few cases of paediatric MDR-TB have traditionally been accurately diagnosed or appropriately treated, but with the imminent roll-out of molecular diagnostic tests,[5,6] these numbers are likely to rise. In addition to the difficulties in diagnosis, treatment is frequently required for greater than twelve months and is associated with significant adverse effects.[7—9]

The aminoglycosides (amikacin and kanamycin), together with capreomycin (a polypeptide), are classified as group two drugs by WHO. These injectable second-line agents are vital for the management of MDR-TB.[2] Although strains resistant to rifampicin but susceptible to isoniazid can be treated with slightly less intense regimens, these rifampicin mono-resistant (RMR) cases are usually treated as MDR-TB in most National TB Programmes. This is due to the limitations of modern molecular diagnostic tests which either do not test for isoniazid resistance[10] or miss a significant proportion of cases which have phenotypic resistance.[11] In most circumstances rifampicin resistance is seen as a surrogate for multidrug resistance.

Both the aminoglycosides and polypeptides are known to have adverse effects that include renal and eighth cranial nerve impairment.[12—14] The effects on the kidneys are thought to be temporary but those on the vestibulocochlear system are permanent.[15,16] Hearing loss related to injectable TB drug use usually starts in the high frequencies and if treatment continues, there is progression to the lower frequencies required for communication; however, in some cases severe hearing loss can develop acutely. Hearing is vital not only for effective communication but also for neurological development. Children with hearing deficits have delayed developmental and communication milestones compared to children with normal hearing.[17—19]

Hearing testing for children is performed for two reasons. The first is to identify and quantify hearing loss to enable the provision of support, education, training and hearing aids. The second is to identify hearing loss early, when it is mild and only at high frequencies, so that treatment, where possible, can be changed to prevent further damage. The testing of hearing is challenging in children. Pure tone audiometry (PTA) is the method of choice for testing adults and allows the testing of different frequencies and amplitudes in both ears independently.[20] PTA is only possible in children on therapy who are able to understand commands and co-operate with testing, which effectively precludes its use in children younger than five years. As young children are at high risk of developing TB following infection and as young children bear the brunt of the epidemic in many settings,[21] this means that many children are excluded from this form of testing. Auditory brainstem response (ABR) testing is the optimal testing methodology for young children[22] but is only available in South Africa in specialist centres. Otoacoustic emission (OAE) testing can assess cochlear patency in younger children and is widely available. OAEs are not fully validated for quantifying hearing loss and do not provide as comprehensive an assessment as PTA or ABR. Although the technology is improving for OAEs, with newer tests able to provide diagnostic evaluations, due to the difference in testing methodology it is not possible to directly compare OAE and PTA. In some studies correlation has been shown to be good between the two types of testing in children,[23] but in others, significant discrepancies are seen.[24] OAE in South Africa is currently used as a screening test.

The frequency and severity of hearing loss is unknown in children treated for MDR-TB with injectable medications. Some data are available for children given these injectable drugs as short antibiotic courses for the treatment of other bacterial infections.[13,25] Some data regarding ototoxicity are available for adults treated for MDR-TB,[26] but few studies have examined the adverse effects of injectable drugs in children treated for MDR-TB. The aim of this study was to determine the frequency and extent of hearing loss in children treated with an aminoglycoside or polypeptide as part of an MDR-TB regimen.

Methods

Setting and standard of care

The Western Cape Province of South Africa had a TB notification rate of 976 per 100,000 in 2009.[27] Amongst children routinely diagnosed with culture-confirmed TB at a tertiary hospital in the Province, 8.9% were identified as MDR.[28] Children with MDR- and RMR-TB present to various regional health centres but once diagnosed and stabilized all children requiring injectable TB medications are transferred to Brooklyn Chest Hospital (BCH). BCH is a specialist TB hospital with a sixty bed paediatric capacity.

MDR-TB (or RMR-TB) is diagnosed as confirmed or presumed disease. A confirmed diagnosis is made when *M. tuberculosis* is isolated using liquid culture with demonstrated resistance.[28] A presumed diagnosis is made if the child had symptoms, signs and/or radiology highly suggestive of TB in the presence of either a drug-resistant source case or when the child was failing first-line TB therapy. Routine hearing testing for children treated with injectable TB medications was introduced in 2008. Children are assessed prior to starting injectable drugs and then monthly. If there are challenges to testing or if abnormalities are found, testing is carried out every two weeks. Where hearing loss is determined, treatment with the injectable medication is (if possible without compromising treatment efficacy) stopped or switched to an alternative medication. Children with severe hearing loss are referred for hearing aids and educational support. Children are treated for MDR- and RMR-TB with amikacin (20 mg/kg once daily via intramuscular [IM] injection) for between four and six months. Children treated for isolates resistant to amikacin are treated with capreomycin (20 mg/kg once daily IM) or streptomycin (20 mg/kg once daily IM) dependent on drug susceptibility test results. Amikacin is used in preference to kanamycin due to the availability of