Aminoglycoside-induced hearing loss: South Africans at risk

South Africa is currently experiencing a TB epidemic with an estimated incidence of 940/100 000 population/year, and the country has been ranked 4th among the 22 high-burden TB countries worldwide by the World Health Organization (WHO).[1] A potentially devastating threat to TB control is the emergence of multidrug-resistant TB (MDR-TB) and, more recently, extensively drug-resistant TB (XDR-TB), mainly as a result of poor drug adherence by TB patients and incorrect management or treatment regimens by health providers; however, direct transmission of drug-resistant strains also plays an important role. The MDR/XDR-TB strains necessitate prolonged chemotherapy for up to 2 years or more, and the use of more toxic second-line drugs including the aminoglycoside (streptomycin, kanamycin and amikacin) and polypeptide (capreomycin) antibiotics. In South Africa, in accordance with WHO guidelines, streptomycin is used for retreatment of TB while kanamycin, amikacin and capreomycin are used to treat MDR/XDR-TB.[2]

Although effective for treating MDR-TB, the aminoglycosides and capreomycin have known dose-related adverse effects, mainly nephrotoxicity and ototoxicity (defined as damage to the hearing or balance functions of the ear). Fortunately, the renal impairment is usually reversible. The ototoxicity, however, is permanent and is due to the death of the outer hair cells in the organ of Corti of the cochlea and type I sensory cells in the vestibular organ (MIM 580000).[3] Aminoglycosides are known to persist in the inner ear tissues for 6 months or longer after administration. These drugs appear to generate free radicals within the inner ear that trigger apoptotic and necrotic cell death of sensory cells and neurons.[4] Streptomycin produces predominantly vestibular damage, while kanamycin and amikacin mainly affect the cochlea.[3] Despite their adverse effects, aminoglycosides are commonly used as short-course antibiotics in developing countries such as South Africa and are, together with capreomycin, important components of the MDR-/XDR-TB drug regimens for 6 months or longer. South Africa is therefore potentially facing the risk of a significant proportion of the population acquiring aminoglycoside-induced permanent hearing loss. Aminoglycoside-induced hearing loss has a major impact on the ability of affected individuals to secure jobs and, since the majority of TB patients are from poor socio-economic backgrounds, there will be increased demands on the country's social welfare and health care budgets.

Risk factors

Risk factors for aminoglycoside ototoxicity include therapy lasting >7 days, prior exposure to aminoglycosides, high daily doses, elevated serum levels, noise exposure, use in the very young or very elderly, and the presence of specific mitochondrial DNA mutations.[5] There are at least 6 mutations described to date (A1555G, T1095C, C1494T, A827G, 961delT and T1291C).[6] The A1555G mutation has been described in numerous populations worldwide, including Chinese, Spanish and Arab-Israeli (MIM 561000). This mutation has also been found in a South African family in which 11 family members were diagnosed with aminoglycoside-induced hearing loss following streptomycin treatment for TB.[7] In subsequent generations of this large family, several of the children will also be at risk of developing aminoglycoside-induced hearing loss. Since these are mitochondrial DNA mutations, all maternal relatives harbour the mutation, and mutation-positive mothers will transmit the mutation to all of their children. Besides this one reported South African family, there are potentially many other families that have one of the known mitochondrial mutations.

It is important to determine the frequency of these mutations in the general South African population to determine what percentage of our population is at risk and to assist health care planners. All TB patients should ideally be tested before they start aminoglycoside therapy to determine whether they harbour any of the known aminoglycoside ototoxicity-associated mutations. Patients at risk of aminoglycoside ototoxicity can then be prioritised for regular audiological monitoring during the course of their treatment; this would lead to more efficient use of South Africa's very limited audiology facilities. Furthermore, if patients are known to have an ototoxicity-associated mutation, early recognition of disease and early treatment is important i.e. to do drug-susceptibility testing immediately that TB is diagnosed, even if it is the first TB episode, and not to wait until patients do not respond to treatment and more extensive disease is present. This could lead to shorter courses of treatment with the second-line injectable agents. A further option not generally considered would be to give preventive treatment to those newly infected with MDR-TB strains, especially children and HIV-infected patients of any age, by giving a combination of two drugs to which the source case is susceptible or naïve for a period of 6 - 9 months, to prevent them from developing MDR-TB (American Thoracic Society/Centers for Disease Control and Prevention (ATS/CDC) guideline – not WHO).[8]

We have developed a cost-effective genetic screening test, based on the SNaPshot technique (Applied Biosystems, Foster City, USA), which can determine the presence of six of the known mitochondrial mutations in a single reaction.[9] It should be noted, however, that these six mutations have been identified in overseas – particularly Asian – populations, and it is therefore likely that the South African population has novel mutations owing to our unique ancestral origins. In the future, once 'local' mutations have been identified, they should be

added to the panel of mutations screened for by the genetic screening test.

Minimising hearing loss

Even though aminoglycosides or polypeptide antibiotics cannot be discontinued in mutation-positive individuals diagnosed with MDR- or XDR-TB, the following strategies can be adopted to minimise the extent of hearing loss in such patients: reduction in therapy time, establishing an evidence-based audiological monitoring protocol, avoidance of excessive noise exposure, avoidance of drugs with synergistic ototoxic effects (e.g. loop diuretics, antimalarials), and the use of antioxidants. A double-blind randomised study of 195 patients demonstrated that administration of the antioxidant aspirin for 14 days protected against development of gentamicin-induced hearing loss.[10] This should be further investigated in TB patients receiving long-term aminoglycoside or polypeptide therapy. Family members of mutation-positive individuals should also be counselled about their risk of developing aminoglycoside-induced hearing loss.

In conclusion: until affordable, less toxic drugs for resistant forms of TB have been developed, we should take cognisance of the fact that the global TB epidemic has also led to an increased burden of aminoglycoside-induced hearing loss, with its economic and social consequences. South Africa needs to take immediate and effective steps to preserve hearing in the thousands of individuals on TB treatment. Introducing genetic testing for patients at risk of aminoglycoside-induced hearing loss should be strongly considered as part of such a strategy.

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