**Introduction**

Otosonic hearing loss refers to a decline in hearing sensitivity resulting from drug-induced damage to the inner ear. Ototoxicity often presents as a symmetric, high-frequency hearing loss, although audiogram shape and severity is highly variable across individuals. Over 100 classes of drugs have been described as ototoxic, the most common of which include loop diuretics, platinum-based chemotherapy drugs, and aminoglycosides (Muld, 2016).

Aminoglycosides are a class of antibiotics that are used in the treatment of gram-negative bacterial infections. The ototoxic and nephrotoxic properties of aminoglycosides have been well-documented. Consequently, these medications are typically reserved for the-threatening infections in the United States and other developed countries. Examples of clinical use include treating chronic lung infections in cases of cystic fibrosis and combat sepsis in preterm infants. Aminoglycosides are more routinely prescribed in developing countries due to their low-cost and high efficacy.

In recent decades, advancements in pharmacogenetics have sparked interest in the effect of genetics on susceptibility to aminoglycoside ototoxicity. The A1555G mitochondrial gene mutation is one genetic variant that has resulted in significant investigative attention. Previous research has suggested that individuals who carry the A1555G mutation are more susceptible to aminoglycoside-induced hearing loss relative to the general population (Sing et al., 2014).

Otosonic hearing loss is often irreversible and, like all forms of hearing harm, it may have detrimental effects on language, cognition, social development, and quality of life. Careful audiologic monitoring of patients at risk for ototoxic hearing loss is vital to reducing these negative outcomes. If associated with increased risk of ototoxic hearing loss, identification of the A1555G mutation calls for more frequent monitoring and, when possible, reduced exposure to aminoglycosides. Understanding the risk factors of ototoxic hearing loss in combination with specific genetic makeup will aid prevention and timely intervention in this clinical population. The aim of this project was to conduct a systematic review on the role of the A1555G mitochondrial mutation in aminoglycoside ototoxicity.

**Methods**

**Search Strategy**

Electronic literature search completed using online databases: PubMed, OAHNL, and EMBASE. Complete search strategy: (drug OR hearing loss) AND genetics AND aminoglycoside.

No language or data exclusions were applied.

**Study Selection**

An initial screening of the articles was completed through an evaluation of titles and years of publication.

**Inclusion Criteria**

- Published prior to completion of the Human Genome Project (2003)
- Evaluation of ototoxic effects of cisplatin/carboplatin or loop diuretics
- Use of animal subjects
- Evaluation of protective agents

**Exclusion Criteria**

- Peer-reviewed studies
- Specifically addressing the A1555G mutation
- Effect of aminoglycoside antibiotics on hearing loss
- Human subjects

Following the first round of exclusions and removal of duplicates, 243 articles remained for review.

Abstracts of remaining articles were then independently assessed by three researchers. All articles were independently assessed by two researchers, with an inter-rater reliability of 79%. All researchers participated in resolving disagreements.

**Critical Appraisal**

Critical appraisals were carried out individually by the three researchers. Twenty percent (24/122) of the articles were evaluated by two researchers as a metric of inter-rater agreement. LEGEND Appraisal Forms from Cincinnati Children’s Hospital were referenced for this process (http://www.cincinnatimatchdentes.org/servic/janderlin-center/evidence-based-care/legend/). Information on study design, sample size, population of interest, prevalence (results), and limitations was gathered from each study and used to make a final determination on the level of evidence.

**Results**

While the aim of the current study was to quantitatively assess the role of the A1555G mutation in aminoglycoside ototoxicity, variability in study designs and outcome measures prevented a meta-analysis of this nature. Nonetheless, results generally support an increased risk of hearing loss following aminoglycoside exposure in individuals with the A1555G mutation.

Three major categories emerged from the current review; studies assessing specific ethnicities, clinical populations involving specific diseases, and neurotics. Articles from Thailand, China, Japan, and the United States were included for review, and it was found that the frequency of the A1555G mutation differs across ethnicities. It is important to note that the studies evaluated did not address regional differences in how frequently aminoglycosides are prescribed, which is an important confounding variable to consider when assessing aminoglycoside ototoxicity across ethnic groups. Studies evaluating at risk clinical populations, such as those with cystic fibrosis and leukemia, and neurotics support the need for increased monitoring for genetic susceptibility to ototoxic hearing loss. This study provides evidence of the variability in prevalence of the A1555G mutation among patients with ototoxic hearing loss and may support an increased risk for hearing loss among those with the A1555G mutation following aminoglycoside exposure.

**Future Implications**

Future studies on this topic should aim to include larger samples sizes and implement replaceable study designs. Comparing audiologic outcomes in individuals receiving aminoglycosides with and without the A1555G mutation using a controlled study design would allow for a more direct assessment of the effect of this genetic variant.

**References**

A full list of references is available upon request. Please contact one of the contributing authors for details.

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