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Aminoglycoside ototoxicity and RNR1 variants

William Newman MD PhD

Manchester Centre for Genomic Medicine, University of Manchester, UK

Disclaimer

- I have just been awarded a grant from the NIHR in the UK to assess the feasibility of a point of care test in neonatal units to avoid gentamicin ototoxicity
- Working with a commercial company genedrive plc who produce the POCT
- I have no financial relationship with genedrive or other COI

Background

- Gentamicin is an aminoglycoside antibiotic that is active against gram-negative bacteria.
- Administered by iv, im or topically
- treatment of neonatal septicemia, especially in premature babies, cystic fibrosis, surgical prophylaxis, neutropenic sepsis
- single injection of gentamicin may cause hearing loss in individuals who have a m.1555A>G variant in *MT-RNR1*.

Evidence for association

- Prezant et al in 1993 described 3 Chinese families with maternally inherited aminoglycoside ototoxicity
- The m.1555A>G conserved variant segregated with the phenotype in these families
- Subsequent reports of the association between this variant and gentamicin induced ototoxicity

Effects of gentamicin in susceptible individuals

- Hearing loss is bilateral, usually severe to profound, and irreversible.
- Occurs in genetically susceptible individuals even in cases where drug levels remain within the therapeutic range.
- Contrast with dose-related ototoxicity – occurs over days
- Nephrotoxicity – usually reversible, dose-related, not associated with mitochondrial variant

Relevant to more than gentamicin

- Six aminoglycoside drugs currently approved for use by the FDA:

amikacin

gentamicin

neomycin

paromomycin

streptomycin

tobramycin

Mechanism of action

- Aminoglycosides bind to 30S bacterial ribosomal subunit to disrupt translation
- Sequence variants in the ribosomal decoding region make mitochondrial RNA more similar to bacterial rRNA, thereby facilitating the binding of aminoglycosides.
- Hair cells in the cochlea are susceptible and irreplaceable

Genetic details

Relationship between variant and ototoxicity

- m.1555A>G variant is nearly always homoplasmic
- Reported complete penetrance when exposed to aminoglycosides
- Results in late onset (>40 years) SNHL in individuals not exposed to aminoglycosides

Allele Frequencies

- In the UK (in 500,000 controls UK Biobank) frequency 0.2% (1 in 500)
- 0.18% in 58,397 Chinese neonates
- Varying frequencies reported in hearing impaired populations

Clinical Presentation

- Potentially neonates are more susceptible
- Other environmental modifiers - noise
- Does not affect vestibular system

Treatment – bilateral hearing aids/ cochlear implantation

Avoidance of ototoxicity

- Opportunistic testing of individuals prior to gentamicin treatment (cystic fibrosis/bronchiectasis patients, presurgical)
- Neonatal Screening (would not capture preterm babies)
- Pregnant mothers (as all offspring would carry the variant)
- Point of care testing

Advice

- WHO "pre-treatment screening is an important consideration to prevent aminoglycoside related hearing loss but given cost and access issues, asking about a maternal family history of deafness may be more practical"

- American College of Medical Genetics and Genomics (ACMG) testing for mitochondrial DNA mutations associated with aminoglycoside ototoxicity may be considered for individuals with a history of use of aminoglycoside antibiotics

- FDA-approved drug label for gentamicin does not include a statement about m.1555A>G.

Many Unknowns

- Relevance of other variants in RNR1 e.g. m.1494C>T, m.961_962deltinsC(n)
- Evidence level – no RCT (no clinical equipoise)
- No historical retrospective studies
- Penetrance – incomplete?
- Population allele frequencies
- Relevance across different age groups
- Relevance across different aminoglycosides

References

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