Aminoglycoside ototoxicity and RNR1 variants

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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


• Dean L. Gentamicin therapy and MT-RNR1 genotype. Medical Genetics Seminars 2012.