Releasing the Genie: Gene Therapy for Otoferlin-related Hearing Loss in Children

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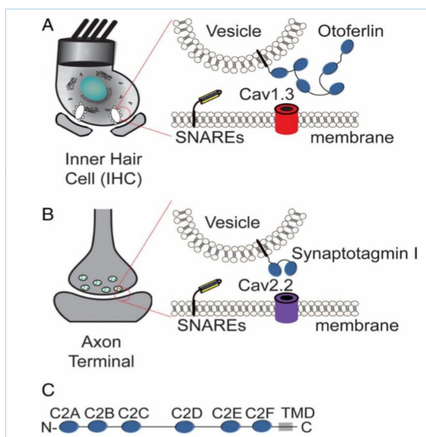
Background

Congenital hearing loss is the most common birth defect occurring in 1 to 3 infants per 1,000 births. There are more than 120 genes associated with congenital hearing loss and there are limited options for the treatment of congenital hearing loss. One of those options is cochlear implantation, which was the last major development for the treatment of children with congenital deafness. Cochlear implants were approved for children in the United States in 1990, six years after they were federally approved for use in adults. Since then, cochlear implants have been life changing for hundreds of thousands of people who otherwise would not be able to hear. As revolutionary as cochlear implantation has been, the hearing it provides is different from the natural acoustic hearing that the rest of the population is born with. The major breakthrough and most recent development in the treatment of congenital deafness is gene therapy. Clinical trials and studies to restore hearing in humans with gene therapy have begun.

The first group of children treated with gene therapy for hearing loss have a specific type of hearing loss. The cause of their deafness is a mutation of the otoferlin (OTOF) gene. The OTOF gene encodes otoferlin, the protein found in the inner hair cells of the cochlea. It is essential for the neuro transmission of sound. Deafness caused by a mutation of this gene is known as DFNB9. It is an autosomal recessive deafness that accounts for 2%-8% of all cases of genetic deafness.

OTOFERLIN



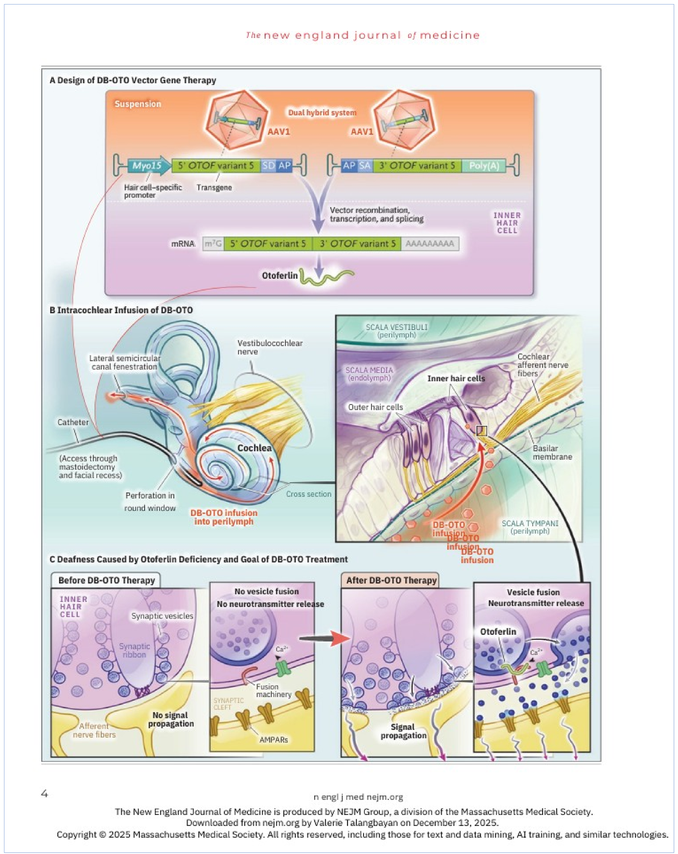
Hams et al, PNAS, 2017

Findings

Early research indicated two primary challenges that needed to be addressed in order for otoferlin gene replacement therapy to succeed.

1) ***How will the replacement otoferlin gene (DB-OTO) be transported to the target inner hair cells of the cochlea?*** By using adeno-associated virus (AAV) vector to deliver the gene. The AAV has been modified to carry a gene/genetic material instead of a pathogen normally associated with viruses.

2) **How can the full-sized ~6 kB otoferlin gene (DB-OTO, *Regeneron*) be delivered into the cochlea when the delivery AAV vector has a limited capacity of ~4.7 kB?** *The solution is to split the gene into two coded, complementary segments. Deliver both segments into the cochlea. Once in the cochlea, the encoded, complementary segments of the otoferlin gene reassemble and the full otoferlin gene (DB-OTO) is introduced to the paralymph of the cochlea.*

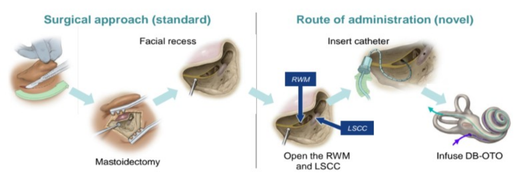


Conclusions

Initially, there were five medical centers working with biotechnology companies, each developing their own gene therapy to treat otoferlin-related deafness, DFNB9. Two of the initial clinical trial sites were in China, one was in France, and two in the United States. Combined, these five centers operated on and treated 19 children with DFNB9 deafness. The gene therapy successfully gave natural, acoustic hearing to all the children in the trials 24 weeks after the infusion. These trials are revolutionary and have ushered in a new era for the treatment of congenital deafness. Since there are more than 120 genes related to non-syndromic hearing loss, additional gene therapies and trials are sure to follow. As of today, U.S. based Regeneron has 10 designated trial sites and is enrolling patients at those sites in the United States, the United Kingdom and Spain.

Providing the highest standard of care for the patient in surgery is the top priority for the perioperative nurse. As patient advocates, perioperative nurses have a responsibility and duty to their patients to continuously learn and familiarize themselves with the most up-to-date scientific, medical, and nursing knowledge and developments. The use of gene therapy for the treatment of DFNB9 deafness is just one example in the burgeoning field of gene therapy. Gene therapy is growing and evolving and will continue to alter the landscape of otolaryngology and other surgical specialties. As this field grows, expands and evolves, so will the role of the perioperative nurse.

- Surgical approach accesses the middle ear, then the inner ear at two points, RWM and LSCC, allowing insertion of a catheter through the round window into the perilymph for DB-OTO infusion



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