Genetics Testing and Early Childhood Hearing Loss – Why is it medically necessary?

Newborn Hearing Screening (NHS) has revolutionized the identification and habilitation of children who are deaf or hard of hearing. Prior to NHS, deaf/hard of hearing children were not recognized until speech delay was evident during the second and third year of life. While most deaf/hard of hearing children are diagnosed as newborns, hearing loss can occur at any age and can have a genetic, infectious, traumatic or autoimmune basis. This genetic hearing loss review focuses on information that can be gained from genetic testing.

For more than half of all deaf and hard of hearing children, a genetic cause can be identified. **Knowing the genetic basis of hearing loss provides a framework for medical management as well as prognostic information.** The American Academy of Pediatrics, the American College of Medical Genetics and Genomics[1] and the Joint Committee on Infant[2] hearing recommend genetics evaluation for children confirmed to have permanent sensorineural hearing loss.

Genetics and childhood hearing loss: A lesson in Precision Medicine

The main intent of genetic testing for a child who is deaf or hard of hearing is optimal care and management, precision medicine, for that child. For a child who is deaf or hard of hearing, there are many questions. Will the child's hearing stay the same over time, or will it decrease to the point where hearing aids will no longer be helpful? Will the child have other health issues? Will this child be one who has an associated condition that can be anticipated? For many patients, genetic testing can provide answers to the questions.

Syndromic versus Non-Syndromic hearing loss:

Nearly thirty percent of all deaf/hard of hearing children will have an associated syndrome. Identification of an underlying syndrome will inform a plan of care. For example, nearly 11% of children who are deaf/hard of hearing have Usher Syndrome. Usher syndrome is a genetic condition where children have hearing loss at birth (congenital hearing loss) and, depending on the type, will develop retinitis pigmentosa in the later part of the first or second decade of life[3]. In children with Pendred syndrome, hearing loss at birth can be associated with thyroid goiter. A genetic diagnosis facilitates proactive medical care by anticipating associated syndromic findings.

Profound hearing loss

For a profoundly deaf child, parents are faced with the decision whether to use cochlear implantation to permit oral communication or not to use cochlear implantation and use American Sign Language (ASL) or other forms of communication. Usher syndrome Type 1 commonly presents with profound congenital hearing loss and balance issues. For the child with Usher Syndrome, vision loss during the later part of the second decade may make ASL difficult. Language outcomes for cochlear implantation are better in children who are implanted during the first year of life but the retinal abnormalities associated with this condition will not be clinically evident at the time parents make such a decision. Genetic testing is the

only way to know whether a young child has Usher Syndrome making the case for use of cochlear implantation more compelling[3].

Mild/Moderate Hearing Loss:

For children with Mild/Moderate Loss, the question is whether a child's hearing loss will progress. Thus, even a child with mild hearing loss should have regular follow up audiology. Genetic testing in many situations can determine the cause of hearing loss and provide prognostic information.

Unilateral Loss:

At one time it was thought that unilateral hearing loss required no intervention. Studies have shown that children with unilateral loss as well as mild loss have more difficulty with school performance[4,5]. For children with unilateral loss, concerns are raised for eventual bilateral loss. Genetic testing in some situations may be able to provide an answer to this question[6].

Cytomegalovirus (CMV):

Evidence of congenital CMV infection is found in 30% of children who are deaf and hard of hearing[7]. Given that oral antiviral treatment may improve both the hearing and neurocognitive sequelae of CMV, early diagnosis of CMV is important for improving outcomes, particularly since there is a narrow window of time, typically before 6 weeks, to discern between a prenatally acquired or a post-natal infection. At this time, the state of Utah has a legislative mandate to test children who are deaf/hard of hearing for CMV[8] and other states are considering such legislation. Genetic testing is also indicated in CMV-positive children as well as the presence of CMV does not exclude a genetic cause of hearing loss.

Recommended Genetics Evaluation of a Child confirmed to be deaf or hard of hearing:

-Comprehensive prenatal, neonatal, postnatal history.
-Audiometric assessment
-Three generation family history with pertinent history for family members with hearing loss, sudden cardiac death, developmental delay, birth defects, common ancestors between parents (consanguinity).
-Physical examination with particular attention to ear structure and other craniofacial anomalies, dysmorphic features, delayed developmental milestones. -CMV culture from urine or saliva, most meaningful prior to six weeks of age
-Genetic testing: single gene testing (typically *GJB2/6* followed by targeted Next Generation Sequencing Panel sequencing recessive (approximately 55 genes), dominant (30 genes), X-linked (4 genes) as well as genes for common syndromic forms of hearing loss.

Genetic Testing:

Genetic testing is best carried out in a setting where stakeholders (patients/parents) are provided both pre-test and post-test genetic counseling. Genetic testing can provide information that is both clear and diagnostic or ambiguous. Families need to be

prepared for results that are unexpected, including diagnosis of a syndromic cause of hearing loss such as Usher Syndrome or Jervell Lange Nielsen Syndrome (profound hearing loss associated with long QTc). It is important to note that genetic testing cannot identify 100% of genetic hearing loss; negative genetic testing does not rule out a genetic form of hearing loss.

Single Gene Sequencing versus Next Generation Sequencing:

Genetics practitioners have moved from testing one gene at a time to performing testing using targeted panels of genes that cause hearing loss by Next Generation Sequencing. Current testing strategies may test more common genes as a first tier of testing and then reflex to a more comprehensive panel of genes. For example, in a child who has bilateral severe sensorineural hearing loss from North America, the likelihood that this child's hearing loss is caused by mutations in the gene *GJB2* is 25% [9,10,11]. Tiered testing may begin with sequencing of *GJB2*, followed by a panel of nearly 100 different genes using Next Generation Sequencing.

Testing may also be tailored to a child's specific clinical features if physical exam is suggestive of a defined diagnosis. In a child who has unilateral or bilateral profound hearing loss, an apparently wide space between the eyes, and a patch of light hair, more targeted testing for the genes associated with Waardenburg syndrome may be the most appropriate course of action.

Family history can suggest recessive, dominant, X-linked or mitochondrial inheritance of hearing loss with recessive forms accounting for up to 85% of hearing loss. For the rare family where both sides of the family have hearing loss, it may be difficult to discern dominant from recessive hearing loss by pedigree analysis alone.

Genetic testing is typically carried out in specific reference laboratories or university laboratories. Use of specific testing sites will vary based on geographic location and practice preferences.

Genetic resources for your region can be identified through the American Board of Medical Genetics and Genomics, www.abmgg.net.

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