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Genetics Of Early Childhood Hearing Loss

The past decade has seen a continued increase in the utilization of newborn screening for hearing loss. As such, the number of infants identified with hearing loss is likewise on the rise. The major impetus behind infant screening has been the improved outcome of speech and language potential in children identified early. There is however, another great advantage in identifying hearing loss early. A significant proportion of early childhood hearing loss has a genetic etiology. The family of every child identified with a significant hearing loss should be offered clinical genetics consultation. A genetics evaluation can provide several important pieces of information to the family and the child's health care providers. First, a specific etiology may be determined. For many families, the "why" is an important question to be answered as its own end.

If an etiology is determined, then specific information can be provided to the family regarding recurrence risks for the immediate and extended family. Also, some of the causes of childhood hearing loss have associated medical conditions. Many of these associated conditions can be medically serious. Knowledge of these risk factors can lead to interventions that prevent morbidity and mortality.

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- 60% of congenital deafness has a primary genetic etiology
- A complete genetics evaluation in a young child with a significant hearing loss has a high diagnostic yield. A specific etiology can be identified in close to 90% of the cases
- Two known causes of early childhood hearing loss – congenital CMV and connexin 26 mutations - each account for about 40% of the identified children

Of the genetic causes of congenital deafness:

- 75% are autosomal recessive
- 20% are autosomal dominant
- 4% are X-linked
- 1% are mitochondrial
- 70% of genetic deafness is non-syndromic, 30% is syndromic
- The empiric recurrence risk (single case without a known etiology) is 10%. Otherwise, recurrence is diagnosis-specific.

What is involved in the evaluation?

The genetics evaluation of a young child is complex, and is best accomplished in the context of an interdisciplinary team. Important components of this team would include specialists in clinical genetics, genetic counseling, otolaryngology, ophthalmology, audiology, speech pathology and vestibular physiology. In addition, this core team should have access to additional pediatric specialists as the work

up progresses. Frequently, consultations are required from pediatric cardiology, nephrology, endocrinology and orthopedics.

The genetics evaluation of a child with hearing loss is ideally performed in stages (tiers). The evaluations should be structured so that tests obtained in higher tiers have a higher expected diagnostic yield, lower invasiveness of testing, better potential of intervention, and easier overall practicality of obtaining the tests. Experience with this approach has a high level of acceptance with third party payers and with families. A general outline of such an evaluation would include:

- **Stage 1:** Medical Genetics, audiology, otolaryngology
- **Stage 2:** Vestibular testing, ophthalmology, CT scan of the temporal bones, serology, urinalysis and serum creatinine
- **Stage3:** Selected DNA tests based on the first 2 stages, electrocardiogram, (if clinical indicators), and electroretinogram (if clinical indicators)

What might be found?

Connexin 26 Mutations

Connexin 26 (GJB2) mutations are found in 40% of infants with congenital hearing loss. This is inherited as an autosomal recessive trait. The phenotype is a non-syndromic hearing loss. Patients have normal vision and vestibular function. The hearing loss is non-progressive most of the time. The hearing loss is typically mild to profound with intra- and inter- familial variability. In a few kindreds the hearing loss is progressive and asymmetric

Congenital Cytomegalovirus (CMV)

The phenotype of an in utero CMV infection can range from asymptomatic to a multiple anomaly complex that includes microcephaly, intracranial calcifications, cognitive impairment, dystonia, optic atrophy, retinopathy, cataracts, and microphthalmia. Congenital CMV can present as an isolated hearing loss. Congenital hearing loss due to CMV accounts for another 40% of early identified hearing abnormalities. While it is not 'genetic' per se, it has significant implications for associated medical problems, progression, and recurrence.

Genetic Syndromes

A variety of genetic syndromes may be associated with hearing loss. Below is a partial list of common syndrome with hearing loss and important medical problems that can be seen with these conditions.

- Branchio-oto-renal syndrome: wide range of renal anomalies, branchial arch malformations
- Pendred syndrome: thyroid goiter due to primary iodine organification defect
- Jervell and Lange-Nielsen syndrome: syncopal attacks, long QT syndrome, sudden death
- Waardenburg syndrome: pigmentary changes, Hirschprung disease
- Usher syndrome: retinitis pigmentosa, vestibular abnormalities
- Mitochondrial based hearing loss: diabetes, neuromuscular disorders, lactic acidosis

Available Resources

Regional Genetic Services

Geneticists, genetic counselors, primary care physicians, families, and others are coming together to identify and address the genetic service needs through participation in the Genetics and Newborn Screening Regional Collaboratives. The regional collaborative effort is funded by the Maternal Child Health Bureau to improve the health of children and their families by promoting the translation of genetic medicine into public health and health care services.

Each region identified priority areas and activities, formed subcommittees, and initiated physician and public education efforts. Several resources are available through the regions including CME opportunities, parent education resources, research studies, small grant programs, and quick access to established networks of local genetic service providers.

The regions are:

1. **New England Regional Genetics Group** (CT, MA, ME, NH, RI, VT)
2. **New York/Mid-Atlantic Region** (District of Columbia, DE, MD, NJ, NY, PN, VA, WV)
3. **Southeastern Regional Genetics Group** (AL, FL, GA, LA, MS, NC, Puerto Rico, SC, TN, Virgin Islands)
4. **Region IV Genetics Collaborative** (IL, IN, KY, MI, MN, OH, WI)
5. **Heartland Genetics and Newborn Screening Collaborative** (AR, IO, KS, MO, ND, NE, OK, SD)
6. **Mountain States Genetics Regional Collaborative Center** (AZ, CO, MT, NM, TX, UT, WY)
7. **Western States Genetic Services Collaborative** (AK, CA, Guam, HI, ID, NV, OR, WA)

National Library of Medicine's Genetics Home Reference

Physicians can help patients and families access up-to-date, reliable, consumer-friendly information about a genetic condition and the basics of genetic science by referring them to Genetics Home Reference, a free, patient-friendly Web site of the National Institutes of Health (NIH).

Website: https://ghr.nlm.nih.gov/

Genetics Home Reference includes over 500 topics on genetic conditions and related genes including congenital hearing loss and genetic conditions that may lead to hearing loss. The site features a richly illustrated tutorial that explains the basics of genetics, from the cellular level on up, and a glossary of genetics terms. The site is regularly updated by scientific staff and reviewed by external experts.

NOTE: This article was prepared, in part, by G. Bradley Schaefer, MD, from the University of Nebraska Medical Center, Munroe-Meyer Institute for Genetics and Rehabilitation. Dr. Schaefer can be contacted as follows: G. Bradley Schaefer, MD, 985430 Nebraska Medical Center, Omaha, NE 68198-5430