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Genetic Testing Hearing Loss: The Challenge of Non Syndromic Mimics

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Abstract

Congenital hearing loss is a common cause of morbidity in early childhood. There are multiple reasons for congenital hearing impairment, with genetic contribution becoming increasingly recognized. Sensorineural hearing loss has classically been viewed as either syndromic or non-syndromic. With the advent of DNA sequencing technology such as NextGen sequencing, a subcategory has arisen, that of non-syndromic mimics (NSM)s. NSMs present initially as isolated hearing loss but as the patient ages other phenotypes become evident. Early diagnosis of these conditions is imperative as patients may suffer significant morbidity and mortality from complications from their hearing loss syndrome. An example is QT prolongation in Jervell and Lange-Nielsen Syndrome. The need for genetic testing and proper genetic counseling is necessary for patients with hearing loss and testing should be done as early in life as possible.

Keywords

hearing loss; Syndromic deafness; Non-syndromic deafness; Non-syndromic mimics; genetic counseling

Introduction

Deafness/hearing impairment is the most common sensory disorder, affecting about 1 in 500 infants. It is also among the most heterogeneous conditions, with both genetic and multifactorial etiologies.[1] The evaluation and management of the children with sensorineural hearing loss (SNHL) requires a multidisciplinary approach. Otolaryngologists, audiologists, and speech and language pathologists are essential to the care of these patients, but

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identifying an underlying genetic etiology is equally as valuable. Genetic diagnosis may allow for prognostication of hearing loss progression, monitoring for associated health features, and providing recurrence chance estimates for families. As such, genetic testing is of significant benefit to the patient and their family (Table).

The genetics evaluation has several steps. To begin, the genetics team determines if hearing loss is the only feature. If hearing loss is the only phenotype, the patient is deemed likely to have Non-Syndromic Sensorineural Hearing Loss (NSSHL). Conversely, the genetics team may identify other features suggesting an underlying genetic syndrome, in which the Hearing Loss (HL) is one of several aspects of the overall syndrome. Often, diagnosing syndromic hearing loss is fairly straightforward as SNHL may not be the major presenting feature. For example, individuals with CHARGE syndrome may have hearing loss, but it is the cardiac and craniofacial malformations that warrant immediate attention.[2] It is similar for many other syndromes that feature hearing loss as part of the clinical phenotype, and while the precise syndrome may not be apparent, the presence of other anomalies make it obvious that the hearing loss is syndromic.[3].

There is, however, a subset of syndromic hearing loss that masquerades as non-syndromic hearing loss, typically because the initial presenting finding is the hearing loss. These non-syndromic mimics (NSMs) can be challenging to recognize. Estimating the occurrence of non-syndromic mimics is difficult, as correct identification is often practitioner dependent. For example,, a thorough dysmorphology exam by a geneticist can improve diagnostic yield by detecting subtle dysmorphisms. An example would be eye measurements showing dystopia canthorum in Waardenburg Syndrome type I, but unless subtle dysmorphisms and physical differences are found on a detailed physical exam, the syndromic nature of these conditions may only become apparent when the other manifestations present.

The classic non-syndromic mimic is Usher syndrome, which includes hearing loss and pigmented retinopathy that leads to significant vision loss. The hearing loss presents in the newborn period and although USH1 is associated with delayed developmental motor milestones, with USH2 there are no other findings to suggest a syndromic form of hearing loss. It is only years later, after the first symptoms of vision loss present, that the diagnosis of USH2 becomes apparent. Prompt genetic testing would avoid this delay.

Today, with the advent of NextGen sequencing, hundreds of genes can be screened simultaneously in an efficient and relatively inexpensive manner. As such, the diagnosis of Usher syndrome can be made very early, long before the development of the vision findings and clinicians are no longer dependent solely on history and physical to make a correct diagnosis. The University of Iowa's OToSCOPE panel includes many NSMs (Usher Syndrome, Pendred Syndrome, Deafness Infertility Syndrome) and syndromes with often subtle phenotypic features (Branchiootorenal Syndrome, Waardenburg Syndrome and Stickler Syndrome). These six conditions make up 21.39% of positive OToSCOPE results. While we do not know how often the clinical diagnosis was suspected prior to genetic testing, our data set shows that significant portions of genetic SNHL cases are non-syndromic mimics. The identification of these entities has significant medical and genetic counseling implications.

Genetic Testing for Nonsyndromic Sensorineural Hearing Loss

SNHL exhibits remarkable genetic heterogeneity. There are over 300 syndromic forms of SNHL, and over 120 different genes associated with NSSNHL. [1]. This heterogeneity is less of an issue for syndromic SNHL, as these patients have additional clinical findings that suggest the diagnosis. In contrast, this heterogeneity presents a significant diagnostic challenge for NSSNHL. While there may be differences in audiogram patterns among some types of NSSNHL (*WFS1* is the classic example), in most cases nothing definitively distinguishes the different genetic types of NSSNHL.[4] This similiarity was a major challenge when Sanger sequencing was with workhorse for genetic testing as the work and cost to screen several genes was prohibitive. Most frequently, analysis was restricted to *GJB2* (Connexin 26) mutations in which accounts for over 30% of singlet cases of severe-to-profound NSSNHL and ~55% of those exhibiting an autosomal recessive pedigree.

The limitation of Sanger sequencing was resolved with the advent of massively parallel DNA sequencing (so called NextGen sequencing), a technology that allows for the testing of many genes (100s-10,000s) simultaneously, at a cost of little more than testing a single gene. This form of testing has revolutionized the evaluation of children with SNHL.[5] Today, unless clinical findings suggest a specific diagnosis, we now order a single genetic test that analyzes ~150 hearing-related genes at a cost of little more than sequence analysis of *GJB2*. This approach has increased our diagnostic yield and provided greater insight into our understandings of the complexity of apparent NSSNHL.[6] Nonsyndromic Mimics NSMs are syndromic forms of SNHL in which the presenting feature is the hearing loss, with no other apparent concerns. However, NexGen sequencing identifies a genetic etiology that has significant implications. Some common nonsyndromic mimics include Usher syndrome, Deafness Infertility Syndrome and Jervell and Lange-Nielsen Syndrome.

Usher Syndrome is one of the most common nonsyndromic mimics. It is inherited in an autosomal recessive manner and can be subclassified as USH1, USH2 or USH3.Infants with USH1 typically have severe-to-profound SNHL and vestibular areflexia, which manifests as delayed developmental motor milestones. These children are excellent cochlear implant candidates. With USH2, the hearing loss is not as severe and these children typically do very well with amplification. With both USH1 and USH2, visual problems develop in the second decade initially as nyctalopia (night blindness) but gradually progressing with loss of peripheral vision until only central vision remains (tunnel vision). If the AAP guidelines are followed, children with Usher Syndrome should be referred to genetics as infants once they fail their hearing screen. As the ocular disease and even the vestibular disease are unlikely to be obvious in infancy, these children are often diagnosed as having nonsyndromic hearing loss unless there is a known family history of Usher Syndrome. These children should not be taught sign language as their only means of communication as future poor vision makes this a poor choice.[7] Furthermore, clinical trial are ongoing for retinitis pigmentosa and Usher syndrome. These typically require molecular conformation (see CLINICALTRIALS.gov).

Deafness Infertility Syndrome (DIS) is another important nonsyndromic mimic. Inherited in an autosomal recessive manner, DIS is caused by copy number variation (CNV) on 15q15.3 that includes the deletion of two genes, *SRTC* and *CATSPER2*. While microarray-based comparative genomic hybridization (aCGH) would likely pick up this genetic change,

CNVs are an important cause of hearing loss and most comprehensive panels also include CNV identification as part of the bioinformatics pipeline. Infants with DIS have no abnormal features except for mild-to-moderate congenital sensorineural hearing loss. And importantly, only males will be infertile. Females with this condition are fertile and only have nonsyndromic hearing loss. Men are unlikely to father a child without using assisted reproductive technologies as they can have low sperm counts and the sperm have poor motility. Intracytoplasmic sperm injections can help affected men achieve conception.[8]

Jervell and Lange-Nielsen Syndrome (JLNS) presents with profound hearing loss at birth. It is caused by missense mutations in two genes, *KCNE1* and *KCNQ1*. Individuals with JLNS also have long-QT syndrome, which can cause significant cardiac events in early childhood. JLNS is thought to be one of the causes of Sudden Infant Death Syndrome. As about half of children with JLNS will have an arrhythmia-related event before age 3, early diagnosis and treatment are important. Indeed, the majority of people with JLNS will not live past the age of 20 without cardiac treatment. Cardiac events are most likely to happen during times of physical or emotional exertion. Cochlear implants should be offered to these patients to treat the hearing loss.

While these three syndromes are among the most common mimics, there are many other well studied NSMs that clinicians will encounter. Wolfram Syndrome, for example, is a complex polyendocrinopathy that typically presents with pediatric onset SNHL. These patients progress to develop diabetes mellitus and optic atrophy by age 15, often with diabetes insipidus, hypogonadism and poor growth. Early diagnosis is essential if the best preventative care is to be provided.[10]

Pendred Syndrome classically presents as moderate to profound down-sloping congenital SNHL associated with enlarged vestibular aqueducts. Affected children may have episodes of vestibular dysfunction as evidenced by sudden difficulty with gross motor skills. By puberty, the patients begin to develop a goiter and require lifelong endocrine care.[11] Branchio-Oto-Renal Syndrome also commonly presents with congenital hearing loss, which can be sensorineural, conductive or mixed. As the name implies, anatomic anomalies of branchial arches and kidneys are also present at birth, but often not recognized at the same time as the hearing loss. [12] It is worth noting the spectrum of some nonsyndromic mimics is broad and molecular sequencing often reveals surprising diagnoses. As such, genetic counseling before and after testing is necessary to ensure optimal patient education.

Genetic Counseling—Genetic counseling during the hearing loss evaluation involves both pre- and post-test genetic counseling. Pre-test genetic counseling sets appropriate expectations for genetic testing, improves a family's understanding of the benefits of genetic testing, and increases uptake of genetic testing for hearing loss [13,14]. One benefit of genetic testing includes the early diagnosis of NMSs to assist in improved health outcomes. While the benefits of early diagnosis of a NSM are evident, the evaluation for such conditions in a child with apparently nonsyndromic hearing loss underscores the importance of thorough pre- and post-test genetic counseling to prepare the family for unexpected health information and to increase understanding of those results.

In 2002, ACMG recommended that pretest counseling for genetic testing for hearing loss include education about the causes of hearing loss, patterns of inheritance, genetic testing options, and discussion of relative options risks, benefits, and limitations [15]. Thorough pre-test counseling should also involve the discussion of possible results from genetic testing and the utility of genetic testing for both the patient's care and for the family.[16] As such, the discussion of possible test results during pre-test counseling should convey the possibility of positive, negative, uncertain, and unexpected results, as well as the implications of each result.

The patient and/or family should understand that a positive result establishes a diagnosis for the patient, provides recurrence risk information for the family, and might provide information about progression of hearing impairment. Families should be informed that negative genetic testing results do not entirely eliminate the possibility of a genetic explanation for the hearing loss, and that uncertain results are typically treated as negative, non-diagnostic results. As NSMs are evaluated with genetic testing panels for hearing loss, families should be prepared for the possibility that a positive result may also be an unexpected diagnosis of a NSM. The discussion of an unexpected diagnosis should include examples of NSMs and associated findings, in addition to the benefits and consequences of an early diagnosis. Discussion of possible unexpected results should also prepare the family for uncertainty about a specific diagnosis as both nonsyndromic hearing loss and NSMs can be allelic disorders (examples: *MYO7A*, *PCDH15*). Finally, pre-test counseling should review that unexpected results may include identifying the patient as a carrier for autosomal recessive NSHL without establishing a definitive diagnosis. Such a thorough conversation is valuable and for some families, a tiered approach to genetic testing (as outlined in ref 15) that limits the possibility of uncertain or unexpected results is preferable.

Upon completion of genetic testing, post-test genetic counseling is required to discuss the genetic testing results and their implications, both for the patient and for the family. Post-test genetic counseling improves the family's understanding of causes of hearing loss and implications of genetic testing results [18,19]. It is especially valuable if a NSM is diagnosed as these children will need clinical evaluations by other specialists.

Conclusions: The genetics of NSHL is complex, with hundreds of genes and every inheritance pattern. While the differentiation between syndromic and non-syndromic forms is often evident based on clinical exam, some syndromic forms become evident only as the person ages and additional findings emerge. Early diagnosis of these NSMs was typically not possible prior to advanced genetic testing. However, while early identification has medical management benefits to the patient and family, it also carries significant potential psychosocial ramifications, reinforcing the need for pre and posttest genetic counseling.

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Table 1

Syndromic Forms od Deafness identified Through NexGen Sequencing.

Condition	Number of cases diagnosed	Diagnostic yield
Usher Syndrome	98	9.98%
Pendred Syndrome or autosomal recessive non-syndromic hearing loss	46	4.68%
Deafness Infertility Syndrome or female autosomal recessive non-syndromic hearing loss	37	3.77%
Branchiootorenal syndrome	16	1.63%
Waardenburg Syndrome	9	0.92%
Stickler Syndrome	4	0.41%