Etiologic Diagnosis of Hearing Loss in 2016 Current Advances & Challenges in Genetic and Viral Diagnoses

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Introduction

Hearing loss is one of the most common congenital deficits with 1 in 500 newborns receiving a diagnosis of hearing loss [1]. As pediatric otolaryngologists we are one of the first clinicians that families see following confirmation of a diagnosis of hearing loss. As such, we play an important role in helping these families navigate this recent diagnosis and counseling them with respect to treatment and diagnostics options for their child.

In our experience, all families presenting with a child with sensorineural hearing loss (SNHL) invariably ask:

Why does my child have hearing loss?

In the period of time following the confirmed diagnosis of SNHL in a child, families strive to accept this diagnosis and their understanding may be clouded by the stages of grief. As a result, presenting both treatment and diagnostic options in a simple and digestible format is imperative to enhance their understanding and facilitate their decision making. This is not always an easy task as it requires that the clinician has both knowledge and comprehension of a continuously evolving diagnostic paradigm, some of which falls outside our immediate zone of expertise. This is increasingly the case as there are novel diagnostic considerations which have enhanced our understanding and diagnostic ability in pediatric deafness.

Despite modern diagnostics, the etiology of SNHL remains elusive in a large proportion of children. That being said we have a number of tools that aid in our determining the etiology of hearing loss. It is important to advise families that at times despite using all tools available to us at present, etiology remains unknown in a substantial proportion of children.

Of the novel diagnostic techniques available imaging of the auditory system has advanced significantly in the last decade. That said, this topic is beyond the scope of this manuscript where the focus will remain on medical diagnoses. The current chapter will focus on our new and evolving knowledge of SNHL secondary to genetic origin and that of congenital cytomegalovirus (cCMV) infections.

GENETIC EVALUATION OF HEARING LOSS IN CHILDREN

As in many domains in medicine there has been a significant evolution in our diagnostic capabilities in the realm of genetic diagnosis. In the early 2000's we remarkably improved our diagnostic capabilities in the setting of non-syndromic hearing loss by our knowledge and ability to perform GJB2 or GJB6 testing. Many centers began using targeted capture algorithms at this stage. In such algorithms, common genes would be analyzed and detected sequentially. Prior to this the genetic evaluation of a child with hearing loss was limited to syndromic genetic

causes and to those children with other phenotypic (clinical or radiologic) features. What has pushed the field over the last decade, is the development of parallel sequencing techniques which, simply put, are a more efficient and economical genetic testing method that we can apply to our children presenting with hearing loss. We will refer to these methods as comprehensive genetic studies and many such clinical tests are commercially available (12 or more at present) with variations in the number of genes tested as well as what they are looking for (i.e. single nucleotide variations, copy number variations etc).

There are published reviews that can aid in how these tests differ and how to choose what is best suited to your clinical population [2]. Regardless of the test one chooses or that is available institutionally, it is important to make understood to families the limits of the tests chosen. Our improved ability to map the genome and test for genetic variants responsible for disease is not however without its challenges and limitations. Simply put, ordering or running the genetic test often becomes the easy and even economical part, while the biggest challenges and expenses lay in the interpretation and the clinical army that is required in order to do so. There are several automated bio-informatic protocols being developed but at present none are sensitive and specific enough to preclude independent analysis of all results.

We will review the current state of the art in the genetic diagnosis of hearing in the framework of the questions most frequently asked by parents.

Through newborn hearing screening we are diagnosing and rehabilitating hearing loss ideally prior to the age of 6 months. As such we may find ourselves in the room with parents and a very young infant who even in the setting of many syndromic causes of hearing loss may not have fully declared all clinical features. In many instances, hearing loss may be the only clinical feature detected. There are many non-syndromic hearing loss mimics. This term refers to a presentation such as the one I have just described where there is indeed a syndromic genetic cause for the hearing loss but that the associated clinical features are not yet apparent. While there are several causes of hearing loss that fall into this category, Usher Syndrome is likely one of the most important ones, given its eventual multisensory deficits including hearing loss, vestibular impairment and visual impairment secondary to retinitis pigmentosa. These causes of hearing loss among others can be identified through comprehensive genetic testing. In the setting of Usher Syndrome in particular, a review of motor milestones and an assessment, if feasible, of balance and vestibular end-organ function may greatly facilitate the interpretation of the genetic results [3]. Jervell and Lange Neilson Syndrome, though very rare can result in sudden cardiac death due to prolongation of the Q-T interval and therefore also must be diagnosed in a child whose only presentation is of hearing loss.

“My child’s hearing loss can’t be genetic, there is no family history”

Given the recessive nature of most non-syndromic causes of hearing loss most families will not have a significant family history of SNHL. When the discussion around genetic causes of SNHL begins many of these families will suggest that it couldn’t be genetic given that there is no family history. Most genetic discussions will therefore begin with an explanation of recessive inheritance and the frequent associated lack of family history this carries with it, with the exception

of families and/or populations with a large degree of consanguinity. It is important to begin your discussion with such an explanation otherwise families may not feel that your discussion of genetics is pertinent to them.

"What is knowing if it is a genetic cause going to change for my child?"

Once families understand that their child may, or is even likely, to have a genetic cause for their hearing loss despite this absence of family history, most will typically ask this question?

In response to this question, the obvious benefits of achieving a genetic diagnosis of hearing loss where one exists include the 1) capacity to recognize and look for other occult phenotypic features 2) impact for future pregnancies in the family 3) knowledge of how this type of hearing loss behaves 'on average'. Currently, with few exceptions, it does not change how we treat the hearing loss. This final point is one that is not insignificant, and in Canada, where there is often no cost to the family associated with performing comprehensive genetic testing, it is the reason many families do not proceed with genetic evaluation.

"How likely is my child's hearing loss to be genetic?"

There is variability in the reported diagnostic rates of genetic testing although the largest study (n=1119 patients with hearing loss) identified a genetic cause in almost 40% [4]. This is within the range of what is reported in other smaller series and is therefore a useful number to use in discussion with families. Achieving this diagnostic rate does not however come from simply ordering the blood test. Such a high diagnostic rate comes only after careful review of the child's family history, phenotype, consideration of their ethnic background and often requires additional testing of the child and their families. Families must understand up front what is required in the interpretation of these tests and in order to obtain accurate results, must be very engaged in genetic testing and willing to return for multiple visits.

In some instances the significance of results requires parents to undergo genetic evaluation to see how the genes in question have segregated (i.e. in the setting of a recessive cause of hearing loss, if both variants came from one parent and that parent does not have hearing loss then those variants are less likely to be pathogenic and responsible for the child's hearing loss). They may also need to bring in siblings as well for clinical and genetic evaluation.

Some of the challenges of determining whether there is a family history of SNHL are the possibility that some family members may not be aware that they have hearing loss. As a result, having parents and siblings obtain audiograms to determine whether they may have unrecognized hearing loss may be important in providing the appropriate context in which to interpret the genetic results.

Often times families who have a poor understanding of what may be involved in order to provide an accurate interpretation of their genetic results, will often fail to follow through on the evaluation required to interpret the results in the clinical context.

"So is my child's hearing loss, genetic or not?"

It is not uncommon for a family of a child who had no abnormalities detected on GJB2/GJB6 testing to have understood that their child's hearing loss was not genetic. This is clearly not the case but speaks to the complexity of the conversations that need to happen around genetic testing.

Prior to ordering testing, an explanation to the family that comprehensive genetic testing may not provide a clear result is important as they will often have the false impression that like other blood tests, the result will either be normal or abnormal. Likewise they should also appreciate that they, their child with SNHL or their other children may be asked to obtain additional tests in order to help clarify the significance of the results.

One of the biggest challenges of comprehensive testing includes the large number of gene variants of unknown significance that may be detected. Even results that suggest that the gene variant is likely pathogenic can be difficult to interpret for the clinician as well as families.

Currently the yield and certainty of diagnosis in the setting of comprehensive testing comes from an intensive and multidisciplinary review of the relevant clinical tests and information regarding the child and their family. This type of approach is particularly important in the setting of results that include the above mentioned variants of uncertain significance or those that are likely pathogenic. There are many expert institutions that are able to do just what I have described and are at the forefront of the genetic diagnosis of hearing loss. However this 'ideal scenario' is challenging for many of us even in large tertiary care hospitals underlining that often our ability to test is greater than our ability to interpret. In this instance, the importance is to develop a paradigm for interpretation and communication of genetic results that is feasible within the confines of the resources available to you.

Current limitations of testing must be acknowledged and communicated to families. In future, more automated bioinformatics pathways may be developed, which will be able to stratify the risk associated with variants of uncertain significance based on gene location and accrued clinical data.

An additional challenge of comprehensive testing is that both the tests we employ evolve to include more genes and our knowledge of the pathogenicity of these gene variants also increases over time. We know more about genetic causes of hearing loss today then we did a decade ago and will know more in a decade then we do now. Families must be aware that while perhaps today we are not able to determine that their child's hearing loss has a genetic basis, there may come a time in the future where we are clearly able to recognize that it is.

In light of this, we may even be tempted to ask ourselves or convey to our patients that perhaps we should wait until we know more? Leaders in the field would argue that we will not know more unless we continue to test and iteratively define the importance of all the variants of uncertain significance that we currently detect and will continue to detect in our hearing loss populations. With this in mind, it is important to consider what our responsibility is towards applying this evolution in testing and knowledge to previously performed tests. To do so would require significant informatics infrastructure at a minimum.

In summary, while comprehensive genetic testing is clearly within the purview of the geneticist and the genetic counselor, this may all seem too much for the otolaryngologist and where we may have once been comfortable with the testing and counseling around GJB2/6, or SLC26A4 testing we may no longer find ourselves as comfortable with comprehensive testing. That being said, at a minimum,

we need to have a sufficient understanding to guide our patients, where desired, through the process and contribute our knowledge of their phenotypic characteristics to the diagnostic team.

Virally induced hearing loss: congenital Cytomegalovirus (CMV)

Congenital cytomegalovirus (cCMV) has long been known and understood as a cause of SNHL. All of us have children who present to our clinic with hearing loss who bear this diagnosis. Typically these children are symptomatic have been affected in multiple ways that are evident since birth and historically they made up a relatively small proportion of our overall hearing loss population. What has come into recognition over the last decade is that these children who came labeled with a diagnosis of cCMV really make up a small, but relatively apparent, proportion of cCMV related SNHL. Importantly, approximately 6-25% of children with cCMV related SNHL have no other signs or symptoms of their underlying disease[5]. These children are often referred to as asymptomatic, which indeed is a misnomer. We have therefore underecognized the prevalence of cCMV in our hearing loss population and may represent up to 20% of nonsyndromic hearing loss cases [5].

SNHL from cCMV has distinct but also variable characteristics which include its propensity to be high frequency (32% have high frequency alone), unilateral (38-50%) or asymmetric and progressive (11-50%) and therefore may be missed on newborn screening. It is estimated that 50% of children with SNHL from cCMV will demonstrate progression [5]. The trajectory to progression is also highly variable and may happen in the newborn period, infancy, childhood or even into the second decade of life. These children therefore require close, longterm audiologic follow-up. Given its characteristics, not surprisingly, with the exception of an absent cochlear nerve, cCMV is one of the leading causes of unilateral SNHL and these children also make up a large proportion of those presenting with asymmetric SNHL.

Confirming a diagnosis of cCMV can be challenging given that testing of a sample obtained in the neonatal period (i.e. first 2-3 weeks of life) is required to be certain that the exposure occurred antenatally versus postnatally. The virus is found in highest concentrations in urine and saliva making these samples ideal for either culture or more commonly PCR detection of the virus. Beyond the first 2-3 weeks of life, we can rely on PCR testing for the virus from the dried blood spot obtained at birth although the sensitivity is poor (34%) and may underestimate prevalence. [5] In many jurisdictions dried blood spots are kept for a number of years and it is useful to find out in your area how to access them for testing. Given the necessity for early sampling, the diagnosis of cCMV is ideally suited for mass neonatal screening which we will hopefully see in the future but is not without challenges.

The detection of cCMV should figure within all of our diagnostic paradigms for children presenting with SNHL and should be one of the first steps in the setting of an idiopathic presentation of SNHL in an infant. In some algorithms, testing for cCMV is considered even prior to genetic evaluation. The clinician's specific capacity to test and diagnose cCMV will depend on the age of the infant presenting, as well as the sample availability the diagnostic capabilities available locally [6].

Identifying CMV as the underlying etiology of the hearing loss has several advantages. Early diagnosis opens the window for the possibility of treatment with antiretrovirals. Six week to 6 months of oral valganciclovir has been used for the treatment of infants less than 30 days of age with symptomatic cCMV and has been shown to improve audiologic outcomes in the short term [7-8]. There are still questions as to the duration of treatment as well as the longevity of the benefit. In addition, the impact of treatment on the audiologic outcomes of children presenting primarily with hearing loss (i.e. otherwise asymptomatic) is yet to be defined and studies in a number of centers may aid in clarifying the benefit of treating these patients. While there are certainly risks to treatment (i.e. neutropenia) it is exciting to consider a potentially treatable cause of hearing loss.

Even in the absence of treatment, identification of cCMV in otherwise asymptomatic children provides the opportunity to look for other subtle sequelae including eye findings and developmental delays. From a hearing surveillance it may alter or direct the frequency of follow up testing given the knowledge that CMV related hearing loss is known to progress at times rapidly, bilaterally, even after many years of stable thresholds.

In the era where studies regarding the efficacy of rehabilitating unilateral/asymmetric hearing loss with cochlear implants are underway, it is reasonable to consider that etiology might influence the long term benefit of unilateral implantation in the setting of cCMV given the propensity for a cohort of these children to progress to bilateral hearing impairment at times with more than a decade of difference between either ear.

Early recognition is key in the setting of cCMV to allow for appropriate audiologic follow-up, to open the door for possible treatment, to help us characterize the presentation and outcomes in these children. The future most certainly holds the answers for the questions we are currently asking about the diagnosis and treatment of cCMV. Gains will hopefully also be made in its prevention through education of pregnant mothers (i.e. avoidance of salivary contact with young children) and possibly even vaccination. The astronomical increase in our understanding of cCMV over the last decade also reminds us that there are likely other etiologies of hearing loss, viral (i.e. Zika virus) and otherwise, that may come into play in our populations of children presenting with SNHL in the years to come.

Summary

As clinicians who look after children with hearing loss we are seeing an ever increasing proportion of children who are able to walk away from our clinics with an etiologic diagnosis.

Identification of etiology is imperative to the advancement of our knowledge particularly as they relate to the outcomes of our interventions. Currently, etiology doesn't predict outcome for hearing rehabilitation, including cochlear implantation. One of the reasons being that the majority of reported outcomes, whether behavioural, electrophysiologic or other, do not conduct specific analysis according to etiology given the large degree of heterogeneity or a large proportion of unknown etiology within these cohorts.

Families will continue to look to us to help them navigate the ever-evolving paradigms for the etiologic assessment of their child with hearing loss. As such we need to keep apprised of the current state of the art in diagnostic as well as draw on the expertise around us as the level of complexity in this domain continues to increase.

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