The Evolution of the Diagnostic Algorithms for Pediatric Sensorineural Hearing Loss

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The incidence of congenital hearing loss is known to be around 1-3/1000 newborns. This incidence increases in older children due to progressive sensorineural hearing loss (SNHL), acquired causes such as meningitis, trauma and due to noise induced hearing loss. As physicians we know that it is extremely important to treat children with hearing loss as soon as possible, in order to maximize their potential for speech and language development. From the parent's perspective however, the first question asked is often "why does my child have hearing loss?"

In order to answer that question we need to look at the shifts in diagnostic algorithms that occurred during the latter half of the 20th century and first decade of 21st century. Prior to the discovery of connexin related hearing loss in the late 90's, the diagnostic algorithm for hearing loss really focused on identifying syndromic forms of hearing loss, in order to provide optimal medical management for the comorbidities associated with syndromic hearing loss. Even after the discovery of connexin related hearing loss, CT scans were the diagnostic modality most commonly used, and genetic tests were scarce, expensive and inaccurate. The diagnostic paradigm favored a "shotgun" type approach and utilized tests such as EKGs (to rule out Jervell-Lange-Nielsen), urine tests, thyroid function tests and other laboratory tests. These were all done in conjunction with and guided by a thorough history and physical examination to evaluate for possible syndromic features and evidence of congenital infections. With the advent of more affordable genetic testing for *GJB2*, and the recognition that it was a major contributor to congenital hearing loss, new paradigms were created that used genetic testing as the first step in the workup of bilateral idiopathic sensorineural hearing loss. In 2005, Preciado *et al*. proposed an algorithm in which single gene genetic testing for *GJB2* was integrated as a prominent feature of hearing loss diagnosis[1]. Their algorithm recommended a *GJB2* screen for all patients with non-syndromic bilateral severe to profound SNHL. They also recommended CT scan for unilateral hearing loss as well as mild to moderate-severe SNHL. *GJB2* screen was also recommended for patients with bilateral SNHL (moderate-severe to mild) who had a negative CT scan. As these algorithms were gaining acceptance and being implemented however, there was increasing recognition that a "one size fits all" approach to the diagnosis of hearing loss is oversimplified. Data emerged showing that in Caucasian populations, connexin testing may be positive in up to 15-40% of patients. However, connexin related hearing loss is only present in 4% of African and 11.5% of Hispanic individuals with congenital hearing loss.[2,3] Therefore, the diagnostic workup must be guided not only by the physical exam, but by the patient's ethnic and demographic makeup.

The diagnostic algorithm for congenital hearing loss continues to vary significantly between institutions and geographic areas. As genetic testing was increasingly implemented, a large amount of data became available regarding the phenotype of patients with different mutations for *GJB2*. Analysis of this data lead to the ability to predict the possible degree of the hearing loss and chances of progression based on specific mutation.[4] This predictive information is now available for a wide variety of genetic diagnoses and a genetic diagnosis can be used to create 3-dimensional representations of gene-specific average audiometric thresholds over time. This allows more informed counseling and preparation of patients. It must be understood however, that single gene testing alone has a low diagnostic yield in most populations of patients. From a population perspective, hearing loss is a genetically heterogeneous condition.

With an explosive revolution in cutting edge genetic techniques such as massively parallel sequencing and targeted genomic enrichment, comprehensive genetic testing (CGT) for hearing loss is rapidly becoming the standard of care for the workup of bilateral sensorineural hearing loss[5]. There are several comprehensive genetic testing panels that are offered which allow for a large number of genes to be tested simultaneously. Some of them test up to 133 mutations associated with nonsyndromic and syndromic hearing loss including Usher and Pendred syndrome. Comprehensive genetic testing provides the single highest diagnostic rate of any available test for hearing loss, especially when testing is guided by the physical exam, the patient's ethnicity and the audiologic phenotype. However, even the most advanced genetic tests provide a diagnosis of the cause of hearing loss in less than 2/3 of patients. Comprehensive genetic testing is limited in availability relative to single gene testing. Although often considered to add cost to the workup, when CGT is used as the initial step in the diagnostic algorithm, it is ultimately less costly than traditional shotgun algorithms utilizing imaging, sequential directed genetic testing, labs and ECG.

The diagnostic approach and expected outcomes can be further refined based on ethnicity and clinical phenotype. For example, in a series of 1119 patients who underwent comprehensive genetic testing, the diagnostic rate was 72% for patients of Middle Eastern ethnicity, but less than 40% in patients of Hispanic ethnicity. Furthermore, in the setting of unilateral hearing loss, comprehensive genetic testing has a diagnostic rate of less than 2% and is not indicated in this setting[6]. Thus the excitement around genetic testing must be interpreted in light of the patient's phenotype.

In situations where comprehensive genetic testing is unavailable or prohibitively expensive, directed genetic testing for common mutations in GJB2/GJB6 may be useful in the evaluation of congenital sensorineural hearing loss. Single gene directed testing, like any portion of the workup should be guided by physical exam and ethnicity. In the absence of CGT, imaging plays a greater role in diagnosis as well as counseling and planning for cochlear implantation. Although of relatively low utility for bilateral symmetric hearing loss, temporal bone imaging is useful in the evaluation of unilateral or asymmetric sensorineural hearing loss, to rule out enlarged vestibular aqueduct, cochlear nerve hypoplasia or aplasia, and other cochleovestibular malformations. Magnetic resonance imag-

ing (MRI) avoids the risks associated with CT scans and ionizing radiation but often requires general anesthesia. MRI will show most cochleovestibular developmental abnormalities as well as assess the status of the VIII nerve complex. Imaging does not need to be performed in the neonatal period as this increases the risk to the patient. (**Figure 1**)

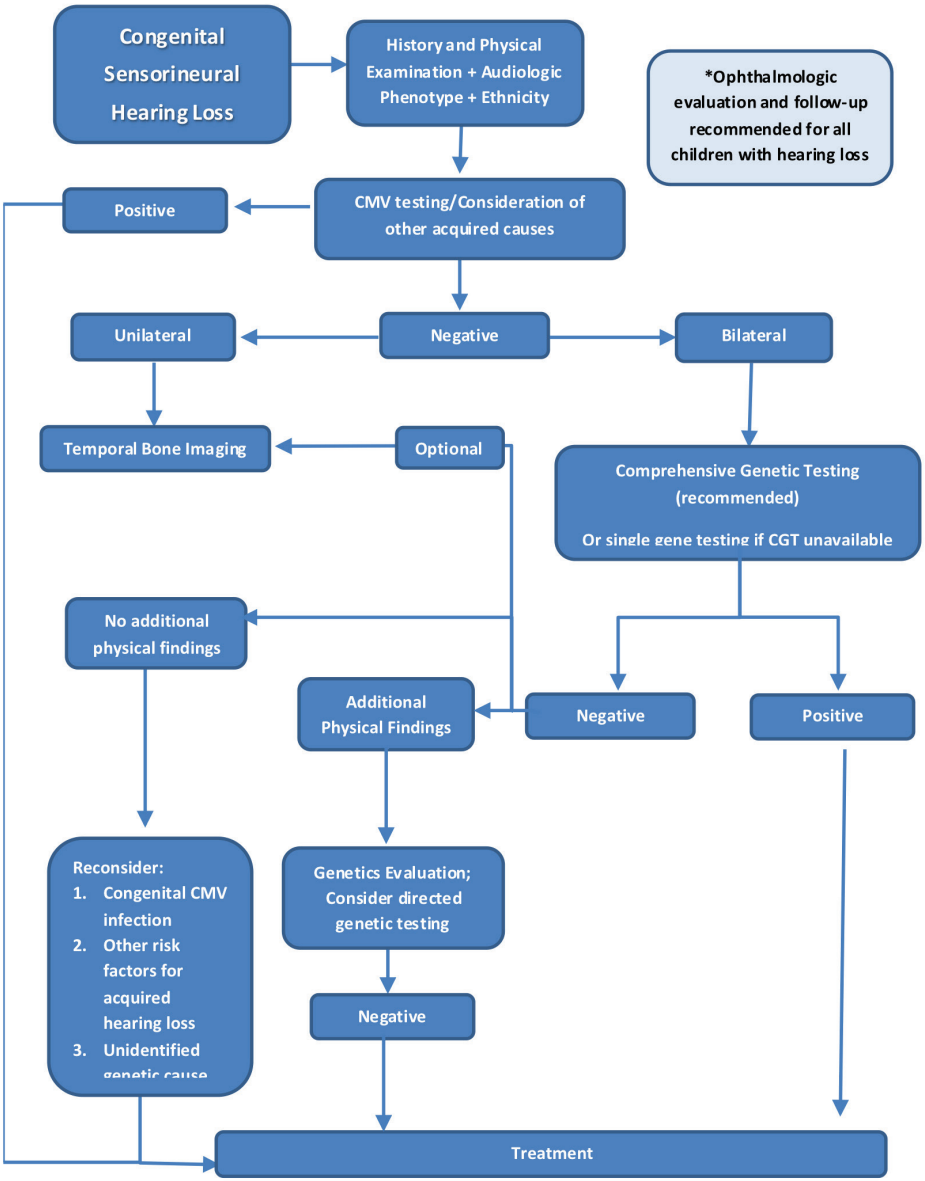

Figure 1. New proposed algorithm for the diagnosis and treatment pediatric SNHL

Acquired causes of congenital hearing loss must not be overlooked. While 60-80% of congenital hearing loss in developed countries is genetic, the opposite is true in developing countries, with up to 80% of patients with congenital hearing loss having acquired causes.

Recently cytomegalovirus (CMV) has become the center of the attention in evaluating acquired causes of congenital hearing loss. CMV is known to cause up to 20% of all congenital hearing loss in the United States. This prevalence is likely higher in Latin American and African countries, given the high seroprevalence of CMV in these populations[7]. Studies have shown that in children with multisystem symptomatic CMV, antiviral therapy with ganciclovir or oral therapy with valganciclovir can result in improvement of audiologic and neurodevelopmental outcomes[8]. These studies were the first to show a treatable form of congenital hearing loss. Although still under investigation, it has even been suggested that treatment with valganciclovir may be beneficial when hearing loss is the only symptom of CMV. Several states in the United States have made it mandatory to test for CMV if a child fails their NBHS. Testing occurs via urine or saliva PCR and has to be done before 3 weeks of age to confirm that the child has congenital CMV. If that is not possible, the newborn screening blood spot can be used for testing. Park *et al* suggested a new paradigm in which CMV testing is in the first step of the workup of idiopathic congenital hearing loss, even prior to genetic testing[9]. CMV associated hearing loss can present in many forms, with bilateral severe to profound, unilateral, mild and progressive forms all being described. The CDC states that as there is no available immunization for CMV, that the "knowledge vaccine" should be applied, advocating that prevention is the key to reducing the impact of this potentially devastating infection. Pregnant women should be educated about the potential consequences of CMV infection and the importance of frequent handwashing and avoiding contact with the saliva and urine of young children.

Other infectious causes of hearing loss continue to be prevalent in developing countries. In one Brazilian study, maternal rubella infection caused 32% of hearing loss in the studied population while 20% was caused by pyogenic meningitis[10]. A two pronged approach of prevention with appropriate vaccination programs and early recognition is vital in combating these causes. Additional viral causes include lymphocytic choriomeningitis virus (LCMV), human immunodeficiency virus (HIV), HSV 1 and 2, measles, varicella zoster, mumps, West Nile and possibly Zika virus. Again, it is imperative that appropriate vaccination and education programs be implemented to reduce the incidence of these potentially preventable causes of hearing loss.

Diagnostic testing has many benefits. First and foremost, it provides piece of mind to parents and provides an explanation for a condition with diverse etiologies. With comprehensive genetic testing, the identification of a specific cause can provide prognostic information related to anticipated progression and allow for advance planning for habilitative options. A genetic diagnosis facilitates genetic counseling and aids in family planning. If a syndromic cause of hearing loss is identified, this diagnosis may allow early intervention for other problems associated with the syndrome. For example, if Usher Syndrome Type 2 is cause of the hearing loss,

the onset of retinitis pigmentosa and visual compromise can be delayed simply by wearing sunglasses. There is also some evidence to suggest that a genetic diagnosis may predict response to cochlear implantation by determining if the causative mutation localizes to the spiral ganglion, hair cells or membranous labyrinth. Genes that localize to the spiral ganglion may predict poorer implant performance[11].

The importance of shared decision making with patients and parents must be appreciated. Parents must have a reasonable understanding of the risks and benefits of diagnostic testing as well as the anticipated outcomes. They must understand that negative genetic testing does not rule out a genetic cause and that as our understanding of genetic hearing loss expands, diagnostic testing will become more accurate.

As the science advances, a genetic diagnosis will facilitate diagnostically guided treatments. Stem cell therapies, gene transfer and silencing and genetic repair techniques are cutting edge treatments that have shown success in animal models. Human trials will likely occur within the next decade. With these advances, the treatment paradigm will shift from amplification to restoration of hair cell function and return to natural hearing. Genetic testing will be the gateway for these treatments.

Until that time however, it is extremely important to stress to the parents the importance of the treatment and habilitation of these children. Treatment begins with identification of hearing loss. In order to identify children and initiate treatment as early as possible, newborn hearing screening protocols have been developed. These protocols aim for diagnosis by 3 months of age to facilitate the initiation of habilitation by 6 months of age. A healthy newborn with no risks factors can be screened by otoacoustic emissions (OAEs) or automated auditory brainstem response (aABR) test. It is important to remember that children with auditory neuropathy spectrum disorder (ANSD) may pass OAE screening but will fail aABR. In addition, while OAEs are easily performed, they are limited to a detection threshold of approximately 40db, thereby failing to detect children with mild hearing loss.

All children with identified hearing loss should be referred to an ophthalmologist. An ophthalmology evaluation may help identify syndromic forms of hearing loss in situations where comprehensive genetic testing is not available. In addition, even children with nonsyndromic hearing loss have a 2-3 fold risk of ocular abnormalities and early identification and treatment allows for optimization of vision outcomes[12]. This is of upmost importance in children with hearing loss, as they will rely significantly more on visual information for communication than their normal hearing peers.

Whatever the type and degree and hearing loss, a child with identified hearing impairment should be treated appropriately by a knowledgeable team skilled in the treatment of childhood communication disorders. The development of children with hearing loss should be closely monitored. It is known that even children with mild and/or unilateral hearing loss are at risk of significant delays in school performance, speech and language acquisition and development and have increased social impairment when compared to normal hearing peers[13,14]. Regardless of the degree or laterality of hearing loss, it is important to offer the appropriate amplification (whether it is preferential classroom seating, FM system, conventional hear-

ing aids, CrOS hearing aids or cochlear implants), educational support, language choice and therapy. Amplification should be considered even in the patient with mild or unilateral hearing loss.

The future of the diagnosis and treatment of sensorineural hearing loss is bright. Comprehensive genetic testing has allowed for improved understanding as to the genetic etiologies of hearing loss. As aforementioned, novel gene therapies are being developed that will one day be used to help restore hair cell function and hopefully we will also be able to improve hearing of children with SNHL caused by congenital CMV with antiviral therapy. The treatment paradigm will soon move beyond amplification to restoration of function.

In summary, the diagnosis of congenital hearing loss has evolved tremendously over the past 60 years. Diagnostic algorithms must be tailored to each individual patient and take into account the patient's audiologic phenotype, ethnicity and the findings on the physical examination.

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