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Diagnosis and Management of Congenital Sensorineural Hearing Loss

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Abstract

Purpose of review Sensorineural hearing loss is the most common congenital sensory deficit, yet the etiology of up to one third of cases remains undetermined. The goal of this review is to outline current diagnosis and management practices in congenital sensorineural hearing loss.
Recent findings Early screening programs have significantly increased the identification of at-risk infants and has allowed for early intervention. Thus, newborn screening is universally advocated. It is important for practitioners to understand and recognize risk factors and possible causes of hearing loss in infants. Additionally, healthcare providers may provide prenatal and postnatal guidance as preventative measures.
Summary Once a child with hearing loss is identified, practitioners must know how best to manage and counsel patients regarding hearing loss. As our understanding of congenital sensorineural hearing loss improves and new genetic discoveries are made, physicians must remain aware of the changes to standard testing algorithms. It is essential that we stay current on advents in massive parallel sequencing and new diagnostic imaging strategies. Finally, knowledge of early intervention programs, hearing amplification technology, and cochlear implantation recommendations is crucial to providing adequate care to our patients.

Introduction

Approximately 1 in 500 newborns are affected with hearing loss, making it the most common congenital sensory deficit [1••]. In many cases of congenital sensorineural hearing loss (cSNHL), it is possible to identify genetic etiologies or environmental/acquired factors; however, the etiology of cSNHL is undetermined or idiopathic in at least a third of cases. Hearing is crucial to our development of language and communication; thus, it is essential for practitioners to identify and manage hearing-impaired children at an early age. The goal of this review is to summarize the current diagnosis and management of cSNHL.

Acquired congenital hearing loss

Acquired cSNHL accounts for 40% of non-idiopathic causes of hearing loss in newborns. There are a wide variety of exogenous factors that contribute to cSNHL in newborns, which can broadly be categorized into infectious, metabolic, toxic, and traumatic (see Table 1). The most common prenatal causes of hearing loss are intrauterine infections. In the perinatal period, hypoxia, hyperbilirubinemia, infection, and medication toxicity are the most significant insults.

Since it was first observed in 1964 [2••, 3], congenital cytomegalovirus infection (CMV) has risen in prevalence as the most common viral infection and the top non-genetic cause of cSNHL. Rates of CMV infection are highest in

Table 1. Exogenous causes of congenital sensorineural hearing loss

Infectious
CMV
Other viruses (herpes, measles, mumps, rubella)
Toxoplasma
Meningitis
Metabolic
Hyperbilirubinemia
Maternal diabetes
Low birth weight/prematurity
Toxic
Alcohol
Drugs
Antibiotics
Ototoxic medications
Traumatic
Noise exposure
Skull trauma
Intracranial hemorrhage

developing countries (1–5% of all births). According to the CDC, the incidence in the USA is 0.8% (CDC web), but is more common with increasing age and parity and decreasing socioeconomic status. A recent systematic review article by Goderis et al. [2••] estimated that 12.6% of infected newborns will develop hearing loss. The hearing loss associated with CMV can be unilateral, delayed in onset, and fluctuating or progressive in nature. The diagnosis of congenital CMV is often missed since the majority of newborns with CMV are asymptomatic at birth and it is not universally tested [4]. It has been shown that there is low sensitivity of CMV testing with PCR on dried blood spots collected for routine metabolic testing in comparison to standard saliva rapid culture [5, 6]. Thus, although it is not currently practical to screen all newborns, several recent studies have shown a cost benefit to selective CMV screening in children with failed hearing screens [7–9]. There are ongoing investigations in this arena, as well as ongoing debate regarding the efficacy of treating CMV in asymptomatic patients with antiviral therapy. In symptomatic patients, it has been shown that treatment with valganciclovir or ganciclovir may improve CMV-related audiologic and neurocognitive outcomes [10, 11]. As there is not yet a vaccine for CMV, prenatal education and awareness remain our strongest defenses against CMV-related cSNHL.

Globally, ototoxicity due to antibiotics is a significant etiology of cSNHL, with aminoglycosides carrying the highest association. It is well known that aminoglycosides target renal and cochleovestibular systems but their precise mechanisms of injury are unknown. With regard to cSNHL, a hereditary component has now been identified. A mutation in the mitochondrial 12S ribosomal gene (A15555G substitution) makes patients particularly susceptible to aminoglycoside ototoxicity [12]. High rates of this mutation associated with aminoglycoside SNHL have been documented in Chinese [13] and Spanish [14] populations.

Genetic hearing loss

The majority (60%) of non-idiopathic cSNHL has a hereditable etiology, and this field continues to expand with the ongoing discovery of new genes.

Syndromic hearing loss

Approximately 30% of all genetic causes of cSNHL are syndromic: correlating to over 300 distinct syndromes [1••]. Syndromic cSNHL is associated with disorders that affect the ocular, renal, nervous, and musculoskeletal systems.

Usher syndrome is an autosomal recessive (AR) disorder that affects both the inner ear and retina. So far, there are 16 independent loci and 13 genes which have been identified and associated with Usher syndrome. Blindness is caused by retinitis pigmentosa and patient may also develop early cataracts. There are three clinical subtypes of usher syndrome based on the severity of SNHL which can range from moderate to profound and may be associated with vestibular abnormalities.

Pendred syndrome is another AR disease, which is associated with iodine organification defects and thyroid dysfunction. Most patients will have enlarged vestibular aqueducts and vestibular dysfunction. The majority of cases are

caused by a mutation in the SLC26A4 gene that encodes the Pendrin protein which is an iodide-chloride transporter. This gene is also responsible for DFNB4 non-syndromic hearing loss.

Jervell and Lange-Nielsen syndrome is defined by cardiac arrhythmias and often associated with prolonged QT syndromes and sudden cardiac death. The majority of cases are caused by an AR mutation in the KCNQ1 gene which encodes potassium channels.

The most prevalent autosomal dominant (AD) diseases which cause cSNHL include Waardenburg, Stickler, and branchio-oto-renal syndromes. Waardenburg is due to abnormalities in neural crest cells and is associated with pigmentation deficits. Stickler syndrome is associated with ocular and skeletal anomalies with a high correlation to Pierre-Robin sequence (micrognathia, glossoptosis, and high arched palate or cleft). Branchio-oto-renal syndrome is often identified by preauricular pits or auricle malformations, enlarged vestibular aqueducts, and renal agenesis.

Non-syndromic hearing loss

Non-syndromic hearing loss accounts for the majority (70%) of genetic cSNHL. The majority of non-syndromic cSNHL (80%) cases are AR (designated "DFNB#"). They are often associated with severe hearing loss with prelingual onset. About 18% of non-syndromic cSNHL is AD (designated "DFNA#") and is associated with progressive with variable severity and is often postlingual in presentation. The remaining 1–2% of cases are due to mitochondrial or X-linked mutations [15]. According to the Hereditary Hearing Loss Homepage (http://hereditaryhearingloss.org), there are currently over 100 genes identified for non-syndromic SNHL. Of note, several genes associated with syndromic cSNHL also manifest as non-syndromic cSNHL.

We briefly review the two most common genes, but refer you to the author's paper on the topic for a more comprehensive discussion [15]. The gene most commonly associated with non-syndromic cSNHL is GJB2 (DFNB1A), which accounts for up to 50% of cases [16••]. This gene encodes the gap junction protein Connexin 26, which plays a critical role in the potassium flow within the cochlea. Currently, the most prevalent allele is 35delG, which causes a frameshift mutation. The adjacent GJB6 gene, which encodes Connexin 30 protein, is also independently associated with cSNHL.

The next most often implicated gene is SLC26A4 (DFNB4), which encodes a chloride and iodide transporter, and is the same gene which can cause Pendred syndrome. Many affected individuals will show evidence of enlarged vestibular aqueducts on imaging and can experience sudden severe hearing loss after minor head trauma [17].

Diagnosis and screening

According to the CDC report, early hearing detection and intervention programs have been established in all 50 states, resulting in 98% of all infants being tested (CDC). Current recommendations state that newborns should be screened by 1 month, with secondary diagnostic testing completed by 3 months in those with abnormal initial exams. With the implementation of universal hearing screening programs, the age of identification of hearing loss has

improved from 30 to 6 months of age [18]. Despite this, screening may still miss patients with delayed onset HL, especially those with SLC26A4 mutations [19]. Most hospitals use a two-tiered approach with both otoacoustic emission (OAE) and ABR [20, 21]. OAE testing is shorter and non-invasive, but remains sensitive to ear canal collapse and vernix as well as middle ear fluid, resulting in higher referral rates requiring further re-screening [22, 23]. Automated screening ABRs have been favored as the initial screening test by many institutions due to its lower false-positive rates and ability to detect babies with auditory neuropathy. Diagnostic ABRs are usually performed after positive initial screens, and thus it is important to minimize false-positive rates and its resulting higher associated costs.

Once a hearing-impaired newborn is identified, a thorough history and physical should be completed by the pediatrician which may provide clues to the cause of cSNHL. Routine standard laboratory testing should not be performed without clinical suspicion, as there is low diagnostic yield [24, 25]. The majority of cases will not have a clear etiology, and thus the remainder of diagnostic tests are based on yield, cost-value, and potential risk to the patient.

Genetic testing for Connexin 26 mutations among idiopathic cSNHL patients is now standard practice. While cost effective, this single-gene testing strategy misses copy number variations, which are often gene-specific [26]. However with new technology, comprehensive genetic testing is now feasible [27]. Massively parallel sequencing (MPS) is based on targeted genomic enrichment and simultaneous isolation of genomic region followed by high-throughput sequencing [28–30]. A recent review analysis by Shearer et al. [31•] showed MPS to be suitable for clinical use with testing sensitivity and specificity > 99%. The overall average diagnostic range of MPS in their review was 41%. As Shearer et al. point out, among the four currently available comprehensive genetic tests available in the USA, there remains a wide variety in the number and types of genes included in each platform. While these tests are available, they may not be affordable to all patients. There has been an argument for selective genetic testing based on ethnicity. Asian patients with mild SNHL had significantly greater yield on genetic testing in GJB2 due to the high prevalence of the p. V371 mutation in this population [32]. Furthermore, a Japanese study showed that ethnic-specific minor allele filtering minimized false-positive results and improved annotation of variants in comprehensive genetic testing [33].

High-resolution temporal bone CT and MRI are important diagnostic tools in determining anatomical anomalies of the inner ear and auditory nerve in infants with cSNHL. CT scans are useful in detecting bony irregularities but do carry risks associated with radiation exposure. MRI is more helpful in identifying cranial, retrocochlear, and soft tissue pathologies, but often requires sedation with general anesthesia.

There is no good evidence to support upfront imaging in newborns with idiopathic bilateral cSNHL. However, there does appear to be high diagnostic yield on imaging in patients with unilateral cSNHL, especially on CT scan [34–37]. Currently, many experts are leaning towards a more cost-effective strategy using a stepwise diagnostic work up that incorporates imaging based on genetic testing [35, 38]. This is based on the low incidence of temporal bone anomalies in patients with GJB2 mutations (Preciado 2005, Lee 2009). Furthermore, Preciado et al. showed that patients with severe to profound SNHL were more likely to have a positive GJB2 mutation than those with mild SNHL [25]. In

patients without GJB2 mutations, imaging appears to be most useful [37]. A study on trisomy 21 patients with cSNHL showed a statistically significant correlation between hearing level and the lengths of patients' vestibules and IACs [39].

Management

Prevention and prenatal education are integral components to treating cSNHL. Proper vaccinations and avoidance of known toxins are important, as 40% of cSNHL cases are due to exogenous mechanisms as previously discussed. Ongoing perinatal and pediatric care is just as crucial. Universal screening for hearing loss has dramatically improved identification of at-risk infants. However, subsequent follow-up and care of these remains problematic with loss to follow-up rates as high as 70% in some areas [40, 41]. Pediatricians working in concert with otolaryngologists and audiologists play a pivotal role in the securing continued care and management of these patients. Often times, the otolaryngologist will take responsibility for decisions on further specific diagnostic tests and audiologic follow-up schedules.

Conservative management involves education and regular follow-up including audiologic evaluation. Physicians should counsel parents on their child's hearing status, possible etiologies, prognosis, and interventional options. They should also encourage noise avoidance and protection against head trauma. Physicians should continue to monitor for middle ear changes including infections or effusions which may contribute to additional hearing loss.

Early intervention programs provide families with resources and support prior to normal childhood education programs and allow for children to join mainstream education when age appropriate [42, 43]. The timing of early intervention is critical in the language and overall development of children, and should be implemented prior to 6 months of age [44, 45]. Exposure to language and communication is vital, as synaptic pruning is completed by age 4–6 years. Furthermore, studies have shown that patients deprived of infant communication may catch up to peers if intervention is done before the age of 2 years [46].

Amplification devices may be offered to infants with mild to moderate hearing loss or unilateral hearing loss. Amplification in a non-invasive approach allows infants to be exposed to a variety of sounds including speech at an early age. However, amplification devices must be chosen and adjusted based on criteria that should be discussed with the audiologist and otolaryngologist. Infants pose several challenges to proper calibration and use of hearing aids. Due to the limitations of current testing methods in infants, it is difficult to accurately determine the threshold and loudness discomfort levels of hearing aids in children [47]. Furthermore, many children do not tolerate wearing bulky devices on their ears and their rapid growth requires frequent replacement of ear molds.

The standard of care in most cases of severe to profound bilateral cSNHL is cochlear implantation. Prospective patients are evaluated with imaging, audiologic testing, and review by a multidisciplinary cochlear implant team. The implant requires a surgical procedure by a trained otolaryngologist and ongoing follow-up with audiology and speech pathology. Cochlear implantation is currently FDA approved for patients with severe-profound hearing loss age

12 months and up. This candidacy criteria is currently being challenged, as there is ongoing debate regarding the timing of implant, severity of hearing loss, and added benefit of bilateral cochlear implantation [48].

The current consensus among experts is that earlier implantation is better, with studies showing that patients implanted before the age of 2 years have improved performance results compared to those implanted later [49, 50]. There have been several studies in small populations which suggest that implanting infants less than the FDA approved 12 months of age may be safe and effective [48, 51, 52]. A recent large multicenter Australian study has shown significant benefit in children implanted younger than 12 months with regard to speech perception, language acquisition, and speech production [53••]. Other investigators suggest that the cochlear implant candidacy should also include patients with less severe hearing loss than specified by the FDA. Carlson et al. showed that children outside of current guidelines, who were not making progress with hearing aids, gained significant benefit in auditory and language measures after cochlear implantation [54]. In a comprehensive systematic review by Forli et al., 19/20 studies documented advantages in verbal perception of noise and sound localization with bilateral cochlear implantation [48].

Compliance with Ethical Standards

Conflict of Interest

Krista Kiyosaki declares that she has no conflict of interest. Kay W. Chang declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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