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Cochlear Implantation in Common Forms of Genetic Deafness

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Abstract

Genetic factors are among the main etiologies of severe to profound hearing loss and may play an important role in cochlear implantation (CI) outcomes. While genes for common forms of deafness have been cloned, efforts to correlate the functional outcome of CIs with a genetic form of deafness carried by the patient have been largely anecdotal to date. It has been suggested that the differences in auditory performance may be explained by differences in the number of surviving spiral ganglion cells, etiology of hearing loss, and other factors. Knowledge of the specific loci and mutations involved in patients who receive cochlear implants may elucidate other factors related to CI performance. In this review article, current knowledge of cochlear implants for hereditary hearing loss will be discussed with an emphasis on relevant clinical genotype-phenotype correlations.

Keywords

Genetic deafness; GJB2; GJB3; Usher syndrome; Wardenburg Syndrome; Jervell Lange Nielson; cochlear Implantation; hearing loss

Introduction

Hearing loss is the most frequently occurring birth defect. The prevalence of congenital hearing loss is estimated to occur in 3 of every 1000 live births.[1] It is further estimated that an additional 1 in 1,000 children will develop hearing loss before reaching school age.[2] Greater than 60% of all prelingually deafened patients are due to hereditary causes with the remaining 40% associated with environmental or iatrogenic causes.[3] Newborn screening tests are now widely used to identify hearing impaired babies and to allow for early intervention. Some patients with hereditary hearing loss are amenable to amplification. However, a certain subset derives no benefit from amplification and must rely on cochlear implantation for auditory input. To this end, we conducted a review of the literature for many of the common forms of genetic hearing loss, including syndromic and non-syndromic genetic deafness, to explore the efficacy of cochlear implantation. The benefits of CI are not currently fully characterized as the literature suffers from a wide array of individual case reports/series involving small study groups. Our literature review is intended to update the reader on the use and performance of CIs in hereditary hearing loss with a discussion of relevant clinical presentations, genetic etiologies, and temporal bone histopathology.

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Connexin 26/Connexin 30

A defect in the connexin 26 (Cx26) protein is the most common cause of nonsyndromic hereditary hearing loss. First mapped by Guilford in 1994[4] and further characterized by Kelsell[5], GJB2, the Cx26 gene, is found on the DFNB1 locus on chromosome 13q12. Among the 21 currently identified connexins, five of which are found in the mammalian cochlea, Cx26 mutation has been reported to cause 50% of cases of nonsyndromic autosomal recessive hearing loss in many populations making investigation of the performance of CIs in Cx26 mutation a top priority.[6, 7] Dominant Cx26 mutations have been associated with syndromic disease with skin disorders. Cx26 mutations have not been associated with vestibular dysfunction.[6] Cx26 mutations usually present without syndromic features although rare non-otologic manifestations have been reported in the literature, such as Keratitis-Ichthyosis-Deafness syndrome and palmoplnantar keratoderma with deafness.[8]

Six connexins make half a channel or connexon. Two connexons create an intracellular gap junction channel, which plays a critical role in electrolyte transportation and communication between cells. It has been suggested that the gap junctions within the ear serve to circulate and buffer the potassium gradient within the spiral ligament and stria vascularis of the cochlea for generation of action potentials in hair cells.[6, 9] In the absence of functional connexons, potassium accumulation and lack of recirculation is presumed to lead to hair cell dysfunction and degeneration.[10] Recent data also suggest that Cx26 channels may be involved in transporting second messenger IP3 for calcium mobilization. Channels with mutated Cx26 block waves of calcium through tissues in vitro.[11] In light of the recent evidence that calcium fluxes may regulate cochlear physiology, it has also been shown that cells expressing heteromeric Cx26/Cx30 channels allow for the spread of calcium much faster than cells with other channels. This suggests that alterations in connexin composition among channels may play a role in regulating intracellular signaling within the ear beyond regulating potassium.[6, 9]

To date, there are over 100 mutations identified for Cx26. One of the most common mutations is the 30delG, also known as 35delG because the deletion can occur anywhere within a stretch of six consecutive Gs.[12] This frameshift mutation results in a premature termination of protein synthesis, accounting for 70% of DFNB1 related hearing loss in Northern and Southern European, American white, and Middle Eastern populations.[6, 13] Furthermore, certain specific ethnic variability of Cx26 mutations has also been ascertained. 30delG is found to be common in whites with a 2-4% carrier rate. 235delC (carrier rate 1-2%) is found in the Japanese. 167delT is predominantly in the Ashkenazi Jewish population (carrier rate 7.5%), and V371 is prominent in Taiwan (carrier rate of 11.6%).[7]

The presence of the Cx26 mutation is not a strong prognostic indicator of auditory perception after implantation.[14-17] Cullen et al appreciated no significant difference in open-set speech perception versus non Cx26 implanted patients.[15] However, Connell et al found that DFNB1 with 30delG patients surprisingly had faster and greater benefits on tests of language and comprehension than matched children with non-syndromic sensorineural hearing loss who tested negative for DFNB1 mutations.[14] DFNB1 patients scored better in the Speech Perception Category scale more consistently and faster than patients without mutation. It is speculated that non-DFNB1 children have a greater complexity of structural and molecular defects as cause of their hearing loss than what is known to occur with the Cx26 mutation, and this subtle difference in cochlear implant performance may be due to preservation of the cochlear nerve and spiral ganglion cells in DFNB1 patients. However, statistical analysis demonstrated that length of implant use was a better indicator of implant performance than genotype.[14] Green et al demonstrated similar results in homozygote and heterozygote 30delG patients.[17] These results were confirmed by Bauer et al who further found that Cx26 patients had better cognitive

performance than other unknown etiologies post implant.[16] In a study of 4 Japanese children with homozygous 233delC of GJB2, a mutation associated with uniform profound bilateral nonprogressive deafness at birth, post implant speech perception scores of all patients were found to be better after cochlear implant than those with no Cx26 mutation. 235delC mutation has been associated consistently with profound hearing loss with little variation among patients. Interestingly, this suggests that those with GJB2 235delC mutations may have greater neural integrity of peripheral and central auditory systems.[18, 19] Not only is this seen with 235delC mutations, a study with the majority of patients being homozygous for 35delG showed better speech and language ability after cochlear implantation in Cx26 patients.[20] The boost in reading performance suggests that the Cx26 mutation is uncomplicated by other pathologies, such as 8th cranial nerve, central auditory system, or higher level cognitive dysfunction.[16] Many others studies have corroborated such results suggesting preservation of the spiral ganglion in Cx26 patients as opposed to those with hearing loss of unknown etiology.[14, 21-24]

Cochlear implantation relies on the integrity of the spiral nerve ganglion and cochlear nerve. Determining the functional status of the nerve is important in evaluating the outcome of cochlear implantation. The percentage of Cx26 patients with temporal bone abnormalities is approximately 8-10%.[13, 25] A temporal bone analysis of a heterozygous Cx26 mutation (35delG and a noncomplementary Cx25 missense mutation), demonstrated intact spiral ganglion cells, no neural degeneration, absence of hair cells in the organ of corti, and agenesis of the stria vascularis.[26] Propst et al. utilized electrically evoked compound action potential testing of the auditory nerve in post implant patients to demonstrate that those with GCx26 related hearing-loss have consistent spiral ganglion cell survival throughout the length of the entire cochlea when compared to non Cx26 hearing loss. One study notes no non-hair cell temporal bone anomalies in CX26 patients.[9] Clinically high rates of success with Cx26 mutations further support the notion of preservation of spiral nerve ganglia and the cochlear nerve.

Usher Syndrome

Usher syndrome was first described by von Gaefe in 1858 and characterized by Charles Usher in 1914. The literature has many names for Usher syndrome including Hallgren syndrome, Usher-Hallgren syndrome, RP-dysacusis syndrome, and dystrophia retinae dysacusis syndrome.[27] Usher syndrome is an autosomal recessive syndromic hearing loss characterized by dual sensory impairment involving both the ears and eyes. Individuals born with Usher syndrome have congenital sensorineural hearing loss with progressive retinitis pigmentosa, leading to degeneration of the retina.[28] This eventually leads to loss of night vision after 10 years of age, restriction of visual fields, and eventually blindness in adolescence. By 2 to 4 years of age, electroretinography can detect abnormalities in the photoreceptors.[29] Usher syndrome is one of the most common causes of deaf-blindness in humans.[30]

Since its discovery, three types of usher syndrome have been characterized: types I, II, and III. Type I Usher syndrome (USH1) is characterized by severe to profound congenital hearing loss, vestibular function characterized by motor development delay in children, and progressive retinopathy with vision loss, decreased peripheral vision, and central acuity in the first decade of life leading to blindness by young adulthood.[27, 29] Low frequency residual hearing may be present at 90-100 dB.[28] Because of this, people with type I Usher Syndrome derive little benefit from amplification and are offered cochlear implantation. Usher type II is amenable to hearing amplification and will not be discussed.

USH1 is the most severe form of Usher syndrome accounting for 30-40%. We and others have shown that the most common USH1 genetic subtype is USH1B, which accounts for between a third and one half of USH1 in UK and the USA.[31] Mutations in the *CDH23* gene at the

USH1D locus are the second most frequent cause of USH1, accounting for between 10 and 35% of the phenotype. Defects in *PCDH15* was found to account for 11% of a USA and UK cohort of USH1, and may be the most common cause of USH1 among Ashkenazi Jewish families, due to a founder mutation. USH1C identified mainly among the Acadian population of Louisiana, has also been detected in diverse ethnic groups. While USH1 syndrome can be identified early by vestibular findings and diagnosed by electroretinography[32], electroretinography is often fraught with technical difficulties, not widely available, and often requires general anesthetic on children.[33] As such, genetic testing has been investigated as an alternative for early identification. While genetic testing shows promise, Liu et al identified only specific mutations in 2 out of the 5 USH1 syndrome patients with CI.[34] Pennings et al identifed mutations in half of his 14 CI patients suggesting more genetic studies are necessary. [35] In a study analyzing the molecular implications of USH1 mutation, it was found that all defective proteins were located within the developing auditory hair bundle, either within the stereocilia and/or kinocilium. The defective proteins in USH1 --myosin VIIa, PDZ-domain-containing protein harmonin, cadherin 23, protocadherin 15, and the scaffolding protein Sans -- are hypothesized to be associated with hair-bundle –linked-mediated adhesion forces. Rodent studies demonstrated mice lacking USH1 proteins orthologues suffer from disorganization of hair bundles.[36]

In an analysis of temporal bones from USH1 patients, examination of the cochlea revealed severe degeneration primarily of the basal turn of the Organ of Corti, atrophy of the stria vascularis, and a decrease in spiral ganglion cells. The cochlear neurons were diminished with an average of 68% neuronal loss compared with age-matched controls. Interestingly, of the 2 patients analyzed, patient 2 had severe saccular macula degeneration, while patient 1 had age-matched degeneration. Only patient 2 was definitively characterized genetically to be USH1D and USH1F. Both patients had the macula of the utricle intact.[37]

In cochlear implantation of Usher syndrome, age appears to be the most critical prognostic factor. Best speech results in Usher syndrome are obtained in those who have cochlear implantation at an earlier age.[32, 33, 35, 38, 39] Moreover, deterioration of vision makes sign language only a temporary solution, emphasizing the importance of cochlear implantation in Usher 1 syndrome.[32, 38] In a study by Liu et al., Usher 1 syndrome patients with congenital deafness, positive electroretinography, vestibular dysfunction, and inability to benefit from conventional amplification were implanted. The patients ranged in age from 2 to15 years old with a mean of 5.4 years. Children implanted before 3 years of age showed the greatest improvement in both open-set and closed-set scores. Of four children implanted before 3 years of age, three had closed-set monosyllable recognition of 76%, two had 80% open set word recognition with lip reading, and one patient had 60% open-set recognition without lip reading. In patients implanted after 6 years old, mean closed-set scores were 54% with only one patient having 82% open-set word recognition with lip reading. No association was made between preoperative mode of communication and postoperative speech perception. Liu et al. conclude that early intervention is critical to developing effective oral-auditory skills prior to visual loss. [33] The results of Blanchet et al. further support the benefit of early implantation.[34] Usher 1 children receiving cochlear implantation between 1 to 3 years old were able to enter mainstream education. Their academic achievement and speech intelligibility was much better than 4-7 year olds receiving cochlear implantation. Adolescents implanted between 14 and 17 were associated with the worst outcomes, i.e. unintelligible speech and inability to achieve open-set perceptive tasks post-implantation. Furthermore, Blanchet found that clinical symptoms were not associated with genotypic mutations; performance post implant was associated mostly with the age of implant.[34] Similarly, Loundon et al. studied a patient group ranging in age from 6 months to 44 years old at of implantation with both Usher 1 and Usher 3 patients.[32] All patients improved in closed speech perception. The best results were noted in patients implanted before 9 years of age. Interestingly, in this series, a group of patients consisting of a 19 year old and

a 20 year old with USH1 and a 44-year-old patient with Usher 3 were implanted. This group of patients all had statistically significant improvement in closed-set words (100%) with variable performance on open-set words (25%-75%). However, a prerequisite for this group was good preimplant oral language, which makes unclear whether the language results are directly attributable to the implant.[32] Young et al. found that variation in benefit of cochlear implantation is not related to the presence of Usher per se, but other factors, such as age at implantation, length of auditory deprivation, and type and intensity of habilitation.[39]

The benefit of cochlear implantation extends beyond the increase in speech perception demonstrated by numerous studies,[32, 33, 35, 38, 39] Godelieve et al. identified a trend via questionnaire suggesting better quality of life, independent living, and speech perception of implanted Usher syndrome patients.[40] The dual sensory nature of Usher syndrome emphasizes the importance of cochlear implantation. Usefulness of sign language will decrease with vision loss making oral communication the primary means of communication.[32, 38, 39]

Mitochondrial DNA

Since the genetic composition of mitochondrial DNA was revealed by Anderson et al in 1981, progressively more information has become known about mitochondrial mutations as the root cause of multiple clinical entities.[41] Mitochondria possess a 16,569-nucleotide base pair double stranded, closed circular molecule DNA encoding multiple messenger and transfer RNA genes, which form the building blocks of the energy-producing core of the cell.[41] The mitochondrial genome is passed down predominantly via the maternal line due to the increased cytoplasmic content of the ovum. It encodes the mechanical framework for the oxidative phosphorylation process resulting in the production of adenosine triphosphate (ATP). Its effective function is critical to nearly all parts of the body, especially those areas with high metabolic needs. Outer hair cells and the stria vascularis have high ATP demands. The hair cells rely on an appropriate endocochlear potential produced by the stria vascularis and its many Na+ K+ ATP pumps. It is hypothesized that mitochondrial dysfunction results in ionic imbalances, cell injury, and then death with concomitant hearing loss. The basal aspect of the cochlea, which is responsible for high frequency hearing, requires even greater metabolic support. As a result, early injury to this area results in the classical high frequency hearing loss associated with mitochondrial dysfunction, which slowly progresses to affect other areas of the cochlear.[42, 43] Subsequent temporal bone studies have supported these findings with evidence of decreased concentration of intact spiral ganglion cells, greater injury to outer hair cells versus inner hair cells, and progression of dysfunction from the basal aspect of the cochlea to the apex.[44, 45]

Mitochondrial hearing loss can be dividing into syndromic and nonsyndromic forms. The syndromic forms associated with cochlear implantation include: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, maternally inherited diabetes and deafness (MIDD) syndrome, Kearns-Sayre (KSS) syndrome, and chronic progressive external opthalmoplegia (CPEO) syndrome.[43] The specifics of each will not be discussed in this review. The nonsyndromic forms are more common and tend to be associated with aminoglycoside hearing loss, especially the 1555 adenosine to guanosine mutation (A1555G).[43, 46] Prezant et al. demonstrated that 1555 codon of the 12s rRNA is a highly conserved area shared among various organisms. As a result, the 1555G mutation creates an analogous bacterial DNA domain, which promotes aminoglycoside binding and subsequent cell injury and hearing loss.[46] Additional mutations have also been identified in A7445G, 7472incC, T7510C, and T7511C in the tRNA gene, MTSS1.[43] These mutations are less common forms of nonsyndromic mitochondrial hearing loss.

Cochlear implantation has occurred in a handful of patients since 1995 throughout the world with multiple case reports describing patient outcomes. Unfortunately, there are no large

outcome studies from any particular group to provide standardized data. Excellent results have been uniformly noted in both nonsyndromic and syndromic forms.

Considering first nonsyndromic hearing loss, Tono et al. implanted a 50 year old individual with an A1555G mutation and sensorineural hearing loss post aminoglycoside exposure 28 years previously.[47] Outcome scores were favorable. The patient had 78% (monosyllable score) and 84% (word score) in sound plus vision field and 54% (monosyllable score) and 76% (word score) in sound alone 10 months postoperatively.[47] Similarly, Ulubil et al implanted a 35 year old individual with an A1555G mutation without aminoglycoside exposure.[48] Audiometric results one month postoperatively demonstrated good open set performance, with scores of 60% on the City University New York (CUNY) and 65% average on hearing in noise test (HINT).[48]

Syndromic outcomes are comparable. There have been reports of at least 4 patients with MELAS syndrome implanted with excellent open set speech recognition. Rosenthal et al. noted 60% CID sentence scores 6 months postoperatively in a 20 year old male.[49] Yasumura et al. implanted a 29 year old female. At 10 months following surgery, word recognition scores improved from 0% to 72% while sentence recognition scores improved from 4% to 94% on closed-set testing; open set word recognition improved from 0% to 44% and sentence recognition improved to 34%.[50] Karkos et al. reviewed two patients implanted in their practice – 31 and 45 year old females.[51] The 31 year old female did not have speech recognition testing but noted significant subjective improvement. Cochlear implant thresholds were obtained and noted to be less than 50 dB from 500 Hz to 4 kHz, which was favorable.[51] No testing was available for the 45 year old female.[51] Positive outcomes have also been appreciated in MIDD syndrome. Raut et al implanted a 42 year old female who demonstrated remarkable clinical progress with Bamford-Kowal-Bench (BKB) auditory sentence scores of 90% postoperatively.[52] Similarly, Counter et al. described a novel mtDNA mutation in a patient with a clinical history suggestive of MIDD.[53] Testing three months postoperatively demonstrated significant auditory progress with CUNY scores increasing from 5% to 84%.[53]

Waardenburg Syndrome

Waardenburg syndrome (WS) is an autosomal syndrome characterized by dystopia canthorum, hyperplasia of the eyebrows, heterochromia iridis, a white forelock, and variable sensorineural hearing loss.[54] WS affects in 1 in 40000 live births and represents approximately 2 to 5 percent of all congenitally deafened children.[55-57] There are four clinical subtypes: type 1 (dystopia canthorum, sensorineural hearing loss, heterochromia iridis, white forelock, hypopigmentation, synophrys), type 2 (type 1 features without dystopia canthorum), type 3 or Klein-Waardenburg syndrome (type 1 features plus hypoplastic muscles and contracture of the upper limbs), type 4 or Shah-Waardenburg syndrome (type 2 features plus Hirschsprung's disease.[54, 57] Deafness in WS may be due to lack of melanocyte pigmentation in the stria vascularis of the cochlea ([Nakashima 1992]) The PAX3 gene, a transcription factor, has been mapped to 2q35 and implicated in WS1.[56, 57] PAX3 interacts with MITF, a promoter for tyrosinase mapped to 3p12-p14, a key enzyme for melanogenesis.[58, 59] Absence of melanocytes affects pigmentation of the hair, skin, and eyes as well as the neural crest cells that migrate and form the basis of the stria vascularis.[58, 60] Temporal bone studies of WS patients have shown atrophy of the organ of Corti and the stria vascularis.[60, 61] Hearing loss has been noted in 35 to 75% of patients with WS1 and 55 to 91% of patients with WS II.[55, 62, 63] Management is variable and includes cochlear implantation for profound sensorineural hearing loss. Radiologic temporal bone studies demonstrate that abnormalities of the bony labyrinth are not common. Malformed and/or absent semicircular canals are most common and require additional surgical vigilance but do not otherwise affect a patient's cochlear implant candidacy.[64]

Outcome studies of WS cochlear implants have demonstrated well above average results in both closed and open set word standardized tests. A review of 7 patients implanted at the University of North Carolina – Chapel Hill showed high levels of speech perception. Five of 7 patients had 100% early speech perception (closed set) with 5 of 7 patients obtaining greater than 50% open set speech perception.[56] An additional retrospective review of 6 WS1 patients from Iran demonstrated a significant improvement in open and closed set speech perception as based on multiple parameters, including the Persian Auditory Perception Test for the Hearing Impaired (PAPT/HI).[65] Four of 6 patients scored greater than 65% on the PAPT/HI while the remaining 2 patients scored 35 and 45%. All children were able to return to regular educational settings. However, there is question of an increased incidence of auditory neuropathy in this patient population, which may undermine implant efficacy. Pau et al. noted 20% of patients in their series of 20 WS patients implanted between 1985 and 2001 had evidence of abnormal electrical auditory brainstem response. They concluded markedly poor speech perception with detection of speech sounds only was consistent with a “true” auditory neuropathy.[66]

Jervell and Lange-Nielsen

Jervell and Lange-Nielsen (JLNS) was probably first described by Freidrich Ludwig Meissner in 1856 when he described a deaf girl who had collapsed and died while being disciplined at school. Anton Jervell and Fred Lange-Nielsen later published the first complete description of JLNS in 1957.[67] JLNS is characterized by a constellation of syncope, sudden death, congenital sensorineural deafness, and cardiac arrhythmias.[67,70] Significant bradycardia can often be observed in patients.[68] Seizures may be observed due to the ischemia during attacks of ventricular tachycardia. QT intervals on EKG are typically greater than 0.44 in males and 0.46 in females. The prolonged QT can lead to ventricular tachycardia, ventricular fibrillation and *torsades des points*, which leads to syncope and sudden death if not treated. 95% of these attacks were triggered by emotional stress, exercise or loud noise, with sympathetic activation as a unifying theme. Swimming is the most probable event accounting for 16% of triggers Prolonged QT intervals may not be present in all situations. Normal QT interval may be present provoked only by stress as stated above.[69, 70] Beta blockers are recommended for control of the arrhythmia. Implantable cardioverter-defibrillator can reduce mortality.[70-73]

The main defect in JLNS is located in the KCNQ1 and KCNE1 (LQT1) gene. Both form the slow component of the delayed rectifier potassium channel complex (90 and 10 percent of cases, respectively). The delayed rectifier potassium channel plays an important role in endolymph potassium maintenance by the stria vascularis and ventricular repolarization by moving potassium ions out of the cell.[71, 74] Temporal bone studies demonstrate the collapse of Reissner's membrane and membranes surrounding the saccule, utricle and ampullae with resulting obliteration of the scala media and endolymphatic compartments of the vestibular end organs.[75, 76]

CI is recognized as an effective therapeutic modality. As previously described, implant electrodes directly stimulate the spiral ganglion bypassing the abnormalities of the organ of Corti. Chorbachi et al presented a case study of three brothers of consanguineous parents. All three were congenitally profoundly deaf and suffered from prolonged QT. The 2 youngest brothers were implanted with good audiometric outcomes, which were not quantified.[70] Yanmei et al. implanted a 3 year old deaf mute female following medical optimization. The authors noted gradual improvement on the categories of auditory performance (CAP) and speech intelligibility rating (SIR). The CAP and SIR were sustained at 7 and 5, respectively, at 36 months follow-up.[73] Daneshi et al implanted three children less than 3 years of age. All three patients were noted to have CAP and SIR scores of 6 and 4, respectively, at 48 months following. All children were able to be mainstreamed into regular schooling. Speech was either intelligible to a listener with limited experience or to all according to the speech intelligibility

scale.[69] However, Green et al. reported a patient was developmentally delayed by 1.5 years despite improvement of open-set word comprehension and expressive language skills.[77] Siem et al reported results of eight children ranging from 17 months to 7.5 years implanted in Norway.[68] Two of eight children died secondary to cardiac events unrelated to implantation. Of the remaining six children, good audiometric results were obtained. Children less than 2 years of age evaluated with the littlEARS test had an average score of 33 of 35. Children greater than 2 years of age tested with a proprietary speech perception test performed at their facility averaged a score of 6 out of 10. Interestingly, all patients were noted to have delayed gross motor development citing possible vestibular involvement. Friedmann et al. noted fibrosis and degeneration of the vestibular epithelium in temporal bone studies performed in the 1960s.[75, 76] However, there is limited knowledge to date on any vestibular compromise that may exist in JLNS.[68]

Extra precautions with the use of anesthetics and certain classes of anti-arrythmics should be considered, especially perioperatively, during cochlear implantation due to the prolonged QT phenomenon.[72] It may be prudent to perform an EKG on those with congenital deafness before operation to identify at risk individuals and prevent possible cardiac complications.[73] Beta blockers should be considered perioperatively. As loud noises may trigger *torsades des points*, a quiet environment, especially during induction, is necessary.[72] With appropriate precautions, cochlear implantation may be performed safely in patients with JLNS allowing for improved audition.

Conclusion

Hereditary hearing loss is a significant cause of hearing impairment. Multiple genetic etiologies of hearing loss have been identified and characterized, including Connexin 26, Usher Syndrome, Mitochondrial DNA, Waardenburg syndrome, and Jervell and Lange-Nielsen syndrome. A review of the literature suggests there are few reasons not to offer cochlear implantation to children, such as advanced age or nonverbal language. Rather, many individuals implanted with genetic forms of hearing loss, especially those implanted at a young age, do remarkably well due to preservation of the spiral ganglion and upper CNS pathways. Future studies of larger cohorts of patients are necessary to support very positive preliminary findings. Additionally, greater focus should be placed on appropriate screening and counseling of individuals with hearing loss. Genetic discoveries are still relatively new in the context of scientific advancement, including the area of Otolaryngology, and there remains significant excitement admixed with hesitation about further exploring the genetic etiologies of many clinical entities.

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