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Causation of Permanent Unilateral and Mild Bilateral Hearing Loss in Children

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Children with permanent unilateral or mild bilateral hearing loss have been a focus of concern by audiologists, educators, and physicians for at least 2 decades. These children are known to be at risk for psychoeducational difficulties. However, despite this concern, little has been learned about the causative factors of these hearing losses and how those factors might be contributing to child development. This review of known causes of permanent unilateral and mild bilateral hearing loss in children is meant to draw attention to the importance of the search for etiologic factors. That is, the identification of the hearing loss should not signal the end of the diagnostic process but, rather, the beginning of a search for causation. With the combined efforts of audiologists, otolaryngologists, pediatricians, geneticists, and other medical professionals, we may enhance our understanding of the primary causes of unilateral and mild bilateral hearing loss and, perhaps, create links between causative factors and psychosocial and psychoeducational outcomes.

Keywords: unilateral; mild bilateral; children; hearing loss; etiology

Unilateral (UHL) and mild bilateral (MBHL) permanent hearing loss have long been implicated for putting children at risk for academic difficulty.[1-7] For purposes of this article, the term "mild" bilateral hearing loss may include what are often termed "minimal" degrees of loss. Bess et al[6] defined minimal degrees of hearing loss as (1) unilateral sensorineural hearing loss, defined as average air-conduction thresholds (0.5, 1.0, 2.0 kHz) 20 dB HL or more in the impaired ear and an average air-bone gap no greater than 10 dB at 1.0, 2.0, and 4.0 kHz and average air-conduction thresholds in the normal hearing ear of 15 dB HL or less; (2) bilateral sensorineural hearing loss, defined as average pure-tone thresholds between 20 and 40 dB HL bilaterally with average air-bone gaps no greater than 10 dB at frequencies 1.0, 2.0, and 4.0 kHz; and (3) high-frequency sensorineural hearing loss defined as air-conduction thresholds greater than 25 dB HL at 2 or more frequencies above 2 kHz (ie, 3.0, 4.0, 6.0, or 8.0 kHz) in 1 or both ears with air-bone gaps at 3.0 and 4.0 kHz no greater than 10 dB. On average, children with these losses have high academic failure rates as compared with those of their normal hearing peers.[1,3,6] The psychoeducational and psychosocial implications of UHL and MBHL are reviewed earlier in this issue by Tharpe.[8] Despite considerable interest in the effects of these losses on child development, little attention has been paid to the underlying etiologies. In fact, contemporary reports of causes of UHL are no more illuminating than reports from the 1960s through the 1980s—before newborn hearing screening. That is, early reports indicated that between 35% and 65% of children with UHL had unknown etiologies.[1,9,10] More recently, in reports from the 1990s, unknown etiology was again reported to account for approximately 35% to 60% of cases of UHL.[11,12] This is indeed surprising given the recent completion of the sequencing of the human genome and other medical advances that have improved our ability to identify genetic, metabolic, and viral causes of hearing loss in infancy. The most commonly reported known etiologies of UHL include viral complications (approximately 25%),[1,9,10,17] meningitis (approximately 15%),[1,9,10] head trauma (approximately 8% to 12%),[1,12] prenatal or perinatal disorders (12%),[4] and genetic disorders.

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Even less is known about the etiology of permanent MBHL primarily because moderate to profound degrees of hearing loss are targeted in our newborn screening programs[13]; thus, lesser degrees of loss are often not identified until school age. The late age of identification of MBHL[12] may contribute to our lack of knowledge about causative factors. That is, in some cases, a delay in identification of hearing loss may limit our ability to interpret etiologic evaluations reliably (eg, cytomegalovirus) or may affect parental memory of possible illnesses or injuries that could account for the loss. For these reasons, much of what we know about etiology of hearing loss in children is related to moderate or greater degrees of loss. However, for every child with bilateral profound hearing loss, 1 or 2 are born with lesser degrees of bilateral or UHL. The US National Health and Nutrition Examination Survey III revealed that 1.5% of school-aged children had bilateral low-frequency hearing loss, and greater than 3% had bilateral high-frequency loss of slight to mild degree[14]; therefore, the large numbers of children with MBHL warrant closer examination of etiologic factors. Table 1 provides a listing of known causes of UHL and MBHL and their prevalence.

Common Etiologies

Although information regarding the etiologies of permanent UHL and MBHL is limited, it is reasonable to suspect that in addition to the few known etiologies of MBHL and UHL some of the same factors that result in more severe degrees of hearing loss can also cause lesser degrees of loss. The following review includes the currently documented causes of permanent UHL and MBHL in children.

Prematurity

Prematurity (ie, preterm births less than 37 weeks) represents a constellation of possible etiologies, and frequently, we are unable to distinguish the various contributing factors to hearing loss in these infants. Morbidity associated with prematurity includes birth asphyxia, intracranial hemorrhage, ototoxic medications, and bronchopulmonary dysplasia, among others.

Several limitations prevent the determination of the prevalence of MBHL or UHL in premature babies. As discussed by Ross et al[15] earlier in this issue, newborn screening programs are designed to identify hearing losses that are of moderate degree or greater. As such, the equipment and protocols used for newborn screening (ie, for measuring otoacoustic emissions and auditory brainstem responses) are designed to identify losses greater than approximately 40 dB HL; therefore, if data are obtained from traditional newborn screening protocols, reports on the prevalence of hearing loss in premature babies will typically not reflect accurate estimations of MBHL and UHL.

One of the few studies reporting on hearing loss by degree in high-risk populations avoided these limitations by conducting behavioral testing when the infants were 8 to 12 months of age.[16,18] The National Institutes of Health Identification of Neonatal Hearing Impairment project examined well-baby nursery graduates with risk factors and neonatal intensive care unit infants (including premature infants) and identified UHL in 3.4% and bilateral hearing loss in 2.2% of babies with high risk factors. Of those with bilateral loss, approximately 65% were of mild degree; however, those numbers may have included infants with conductive as well as permanent loss. Of those infants predicted to have permanent bilateral hearing loss, there were approximately equal numbers of ears having mild, moderate, severe, and profound degrees of loss.[18]

Herrgård et al[17] prospectively followed 58 premature (≤32 weeks) infants until 5 years of age. They found approximately 5% of these infants had permanent MBHL or UHL.

Genetic

Connexin. More than 150 genes for syndromic and nonsyndromic deafness have been "mapped" to chromosomal regions, and of these, at least 80 have been identified. However, by far, connexin mutations are the most common cause of genetic hearing loss in the United States. Mutations involving the GJB2 gene that encodes the gap junction protein connexin 26 are the commonest form of deafness in many populations, accounting for 30% to 40% of genetic cases.[19,20] Members of the connexin gene family are thought to participate in the recycling of potassium back into the cochlear endolymph, a critical step in the physiology of sound perception.[19]

Most connexin deafness reported thus far has been profound in degree, but the murine model (mice used as a disease model) provides a clear precedent for reported nonpenetrance at birth,[21] suggesting the opportunity for less severe degrees of hearing loss. Furthermore, Wake et al[22] found a

Table 1. Known Causes of UHL or MBHL and Prevalence Estimates

Cause	Frequency of Occurrence	Reference
Genetic		
Connexin	Accounts for 30% to 40% of all genetic hearing loss; 1% to 16% of these cases are estimated to result in MBHL.	Liu et al[84] Wake et al[22]
Mitochondrial	Accounts for less than 1% of prelingual deafness and 5% of postlingual, nonsyndromic hearing loss; 21% of these cases are MBHL.	Marazita et al[85] Jacobs et al[86]
Enlarged vestibular aqueduct	Accounts for 5% to 7% of all cases of unknown etiology; 38% of children with EVA have MBHL, an additional unknown number will have UHL.	Callison and Horn[27] Arjmand and Webber[87]
Sudden	Three percent to 5% of all cases occur in children; as many as 98% have UHL.	Wynn et al[35]
Auditory neuropathy	Accounts for less than 1% of all pediatric hearing loss; approximately 33% of cases have borderline normal, MBHL, and there have been few reports of UHL.	Foerst et al[40] Madden et al[88]
Noise induced	Approximately 10% of all children in the United States have noise-induced hearing loss; approximately 20% of these are MBHL.	Niskar et al[45]
Viral/bacterial		
Mumps	Accounts for approximately 2% of childhood hearing loss; 80% to 95% of these cases are UHL.	Unala et al[89]
Otitis media	Five percent to 20% of all cases of otitis media will result in SNHL; the majority of these cases are bilateral, high-frequency SNHL, with some reports of UHL.	Mutlu et al[65] Arnold et al[90] Vartiainen and Karjalainen[91]
Congenital CMV	Thirteen percent to 24% of all children with asymptomatic CMV and up 40% of children with symptomatic CMV will have SNHL; 17% of the asymptomatic and 12% of the symptomatic cases are MBHL; 52% of the asymptomatic cases and 33% of the symptomatic cases are UHL.	Ogawa et al[72] Fowler et al[73] Dahle et al[92]
Meningitis	Ten percent of all children with bacterial meningitis are left with SNHL; 4% to 30% of these are UHL; 14% are MBHL.	Fortnum and Davis[74]
Prematurity	Five percent of premature infants have MBHL or UHL.	Herrgård et al[17]

Note: MBHL = mild bilateral hearing loss; SNHL = sensorineural hearing loss; UHL = unilateral hearing loss.

large proportion (16%) of their cohort of Asian children with slight to mild bilateral sensorineural hearing loss were homozygous for the V37I change in the GJB2 gene. They concluded that this change is a mutation associated with hearing loss and is a common cause of slight to mild sensorineural hearing loss in Asian children. Similarly, Kenna et al[23] reported on a cohort of children with biallelic (ie, both alternative forms of the gene) Cx26 mutations (M34T or V37I) and found that they had a slightly higher incidence of mild degrees of hearing loss (including UHL) than previous studies indicated. Others have reported hearing loss resulting from GJB2 mutations in the mild hearing loss range, including high-frequency hearing loss (4 to 8 kHz).[24]

Mitochondrial 12S ribosomal (rRNA). In the United States, 10% of those with hearing loss resulting from pharmacologic ototoxicity have mutations involving the mitochondrial 12S ribosomal (rRNA) gene, including the A1555G substitution, which is associated with extreme sensitivity to aminoglycoside ototoxicity.[25] This mutation is very common in China, accounting for up to a third of all patients with aminoglycoside ototoxicity.[26] Individuals with these mutations have a higher susceptibility to aminoglycosides at lower dosages than the average population.

Ototoxicity is the ability of a chemical or drug to cause damage to the inner ear or, on rare occasions, the central auditory pathway. The mechanism for how aminoglycosides get into hair cells remains unknown, but it is possible to have hair cell loss without associated hearing loss. The hearing loss associated with ototoxicity is typically high frequency and bilateral.

Enlarged Vestibular Aqueduct Syndrome

A well-known cause of UHL and MBHL in children is enlarged vestibular aqueduct (EVA) syndrome. The vestibular aqueduct is the bony canal extending from

the vestibule to the endolymphatic sac in the temporal bone and contains the membranous endolymphatic duct. Along with the endolymphatic sac, the vestibular aqueduct is thought to help regulate the concentration of ions in the cochlear fluids. It is speculated that an EVA will result in the expansion of the endolymphatic sac and duct. Such an enlargement may result in a chemical imbalance, causing hearing loss.

Typically, the diameter of the vestibular aqueduct at its midpoint ranges between 0.5 and 1.4 mm. A commonly accepted definition of EVA syndrome is a diameter greater than 1.5 mm at the midpoint. The diagnosis of EVA is achieved with the use of computed tomography imaging of the temporal bones and magnetic resonance imaging.

This particular cause of hearing loss has been reported to account for 5% to 7% of hearing loss that has previously been classified as having unknown etiology[27,28] and is the most common form of inner ear malformation associated with sensorineural hearing loss.[29] A recent study found EVA in 32% of children with sensorineural hearing loss in their cohort[30]. However, these authors defined a large vestibular aqueduct as one in which both of its widths were above the 95th percentile (>1.9 mm at the operculum and/or >0.9 mm at the midpoint) of the control group, a definition that is not yet widely accepted and may overestimate the incidence of EVA. EVA malformations have been linked to Pendred Syndrome, branchiootorenal syndrome, CHARGE Association, and Waardenburg Syndrome.[31]

Hearing loss that occurs with EVA has a sudden onset or gradual progression. The disorder is twice as likely to be bilateral than unilateral and will often result in some degree of hearing loss ranging from minimal to profound.[32] Children who have been diagnosed with EVA are strongly encouraged to protect their remaining hearing by taking precautions against damaging the delicate structures of the vestibular aqueduct. Such precautions include avoiding contact sports and extreme changes in barometric pressure.

Sudden Idiopathic

Sudden hearing loss has been characterized as hearing thresholds of 30 dB or greater at 2 or 3 consecutive frequencies.[33,34] Anecdotally, patients with sudden hearing loss report a decrease in hearing overnight or a rapid progression in hearing loss over several days. Furthermore, the hearing loss typically occurs in only 1 ear. Only 2% of patients with sudden hearing loss are affected bilaterally. The exact cause of sudden hearing loss is only found in approximately 10% of patients,[35] with the rest being categorized as sudden idiopathic. For those who receive a definitive diagnosis, viral and vascular factors, membrane puncture, and autoimmune disease are most often implicated.[34]

The prevalence of sudden hearing loss in children is lower than in adults. Specifically, only 5% of all cases of sudden hearing loss occurs in patients under 21 years of age,[36] and only 3.5% occurs in patients under 14 years of age.[37] Treatment options for sudden hearing loss are limited because the exact etiology is often unknown; however, common treatments include the use of vasodilators, steroids, diuretics, and anticoagulants. Spontaneous recovery is common among patients with sudden hearing loss. In fact, the rate of spontaneous recovery has been reported to occur in as many as 65% of patients with sudden loss.[38] Roman et al[33] reported that partial hearing recovery occurred in approximately 29% of their small sample of children with sudden hearing loss. Of those, half had their hearing loss improve to a level of a mild degree of loss. In addition, an absence of recovery was significantly correlated with 3 factors: severe initial hearing loss, association of vertigo, and "downward" sloping audiometric curve.

Auditory Neuropathy/Dyssynchrony

Auditory neuropathy/dyssynchrony (AN/AD) is an auditory disorder in which patients typically demonstrate hearing loss for pure tones, impaired speech perception that is out of proportion to pure tone loss, absent or abnormal auditory brainstem responses, and normal outer hair cell function as measured by otoacoustic emissions and cochlear microphonics. The audiometric configurations associated with AN/AD vary considerably, from normal pure tone sensitivity to profound loss, and UHL and MBHL have been reported.[39,40] In such cases, pure tone thresholds are very poor predictors of the degree of difficulty or handicap that a child may be experiencing. However, on rare occasions, speech perception ability may be only minimally affected, at least in optimum acoustic conditions.[41]

It appears that there may be many causative factors associated with AN/AD, including mutations of the otoferlin gene (OTOF),[42,43] hyperbilirubinemia,[43,44] asphyxia,[43,44] and prematurity.[43] Several possible sites of lesion have been posited for AN/AD, including abnormality of the peripheral auditory system localized

to the inner hair cells, the eighth nerve, or the synapse of the inner hair cells and eighth nerve.[43]

Noise Induced

Hearing loss caused by noise exposure is not limited to the adult population. In fact, 5.2 million, 6 to 19 year olds (or approximately 10% of children surveyed in this age range) have hearing loss related to noise exposure[45]; however, the authors do not indicate if these losses are temporary or permanent in nature. In addition, evidence of high-frequency hearing loss in nearly one third of a cohort of college students has been reported.[46] Noise-induced hearing loss occurs as a result of chronic or acute noise exposure.

Genetic factors have also been implicated in the susceptibility one has to noise.[47,48] Chronic exposure has been characterized by prolonged exposure to sounds that exceed 85 dP SPL for an 8-hour period, and acute noise exposure occurs as the result of events such as an explosion or gunshot close to the ear. Acoustic trauma results in immediate hearing loss, whereas hearing loss from chronic noise exposure occurs gradually over time.

Hearing loss of this nature is initially restricted to the high-frequency regions (3 to 6 kHz) and eventually, with additional exposure, extends into the lower frequencies. Hearing loss secondary to noise exposure occurs as a result of damage to the hair cells of the cochlea. Specifically, changes in sound pressure create a shearing force on the stereocilia of the hair cells lining the basilar membrane of the cochlea, which leads to our perception of sound. Excessive force caused by high levels of noise can lead to cellular metabolic overload, cell damage, and cell death resulting in hearing loss.[49]

Possible environmental sources that may contribute to noise-induced hearing loss in children include fireworks, lawn mowers, and toys.[50,51] In fact, several popular toys such as bike horns, toy cell phones, and arcade games have been shown to produce high enough intensity levels to harm hearing.[51,52] In addition to toys, children may be at risk for noise-induced hearing loss from prolonged use of personal audio players and attending musical concerts.[51] Portnuff and Fligor[53] recently examined the safety of listening to the popular iPod device. By using current Occupational Safety and Health standards,[54] they concluded that users can listen for 4.5 consecutive hours with the volume set at 70% without risk of hearing loss if using the stock ear phones that are supplied with the device. The allowable number of safe listening hours was shown to decrease with increased volume and with different forms of headphones (ie, ear buds vs supra-aural headphones). The authors encourage the data to be interpreted with caution because not everyone has the same risk of hearing loss from prolonged noise exposure and there is no way to predict those who have more or less sensitive ears.

Viral/Bacterial

Mumps. The mumps virus was a common cause of acquired UHL before the introduction of the mumps vaccine in 1967. Most developed countries have experienced a 90% to 95% decrease in the incidence of mumps as a result of the availability of immunizations[12]. However, reports of recent outbreaks of mumps have appeared in the United States, the United Kingdom, and other developed countries.[55,56]

Histopathologic examination of the temporal bones from individuals who suffered hearing loss after infection with mumps indicates a severe atrophy of the organ of corti and stria vascularis. Endolymphatic hydrops have also been noted, along with damage to the endolymphatic duct and fibrous tissue in the endolymphatic sac.[57]

Otitis media. A rarely reported but viable cause of acquired sensory UHL or MBHL is middle-ear disease with effusion. The mechanism causing this drop in bone-conduction threshold is unknown. However, some have speculated that bacteria travels from the middle-ear space through the round window, causing damage to the basal end of the cochlea.[58-60] It has also been proposed that the accumulation of fluid in the middle space reduces oxygen to the cochlea via the round window affecting cochlear function.[61,62]

An early history of ear disease in young children, especially when combined with a history of multiple sets of myringotomy tube insertions, appears to be a prerequisite to hearing loss in the high frequencies.[63,64] Mutlu et al[65] found evidence of temporary and permanent sensory hearing loss at 1 or 2 high frequencies in 9% of a cohort of children with otitis media with effusion. The hearing loss was most frequently observed at 2 kHz, which is consistent with damage to the region of the cochlear basal turn.

Congenital cytomegalovirus. Congenital cytomegalovirus (CMV) is the leading cause of nongenetic sensory hearing loss and the leading cause of unilateral prelinguistic hearing loss in children.[66] CMV infections vary in frequency according to maternal age, race, and socioeconomic status. Congenital infection

occurs in 0.2% to 2.5% of all live births,[67] with an average incidence of 1%. This translates to approximately 10 000 to 80 000 infants born in the United States each year with congenital CMV infection,[68,69] making CMV the most common congenital viral infection.[70]

Initial CMV infection, which may have few symptoms, is always followed by a prolonged, inapparent infection during which the virus resides in cells without causing detectable damage or illness.[71] Severe impairment of the body's immune system by medication or disease increases the likelihood that the virus will be reactivated from the latent or dormant state. Infectious CMV can be shed in the bodily fluids of any previously infected person and thus may be found in urine, saliva, blood, tears, semen, and breast milk. The shedding of the virus may take place intermittently, without any detectable signs and without causing symptoms. Recurrent disease rarely occurs unless the immune system is suppressed as a result of therapeutic drugs or disease. Therefore, for the vast majority of people, CMV infection is not a serious problem. However, CMV infection can be harmful to certain high-risk groups, including the unborn baby during pregnancy.

The hearing loss associated with CMV can range in degree, can be unilateral or bilateral, and can have onset months or years after birth.[72,73] Only approximately 14% of the infections are identified at birth, with the remaining 86% being asymptomatic.[21] In cases not recognized at birth, it can be difficult to impossible to diagnose because of the high incidence of postnatal infection. Nance[66] has speculated that the neurologic deficits associated with CMV may be to blame for the poor academic performance of children with UHL secondary to infection, rather than the hearing loss per se.

Meningitis. Hearing loss is the most common complication of bacterial meningitis among children. The incidence of hearing loss with streptococcus pneumoniae is greater than neisseria meningitidis (35.9% and 23.9%, respectively).[75] UHL occurs in 4% to 30%[74,75] and MBHL in approximately 14% of those with bacterial meningitis.[76] Although most cases of postmeningitic hearing loss are permanent, there are reported cases of spontaneous recovery.[75] In fact, one study reported approximately 10% of subjects had a rapid recovery of hearing.[77] The hearing loss is caused by cochlear damage early in the illness, with at least one report indicating that the hearing loss occurred within 6 hours of the diagnosis.[77] The cochlear aqueduct, which links the scala tympani to the subarachnoid space, is the likely conduit for transmission of bacteria to the cochlea. Although viral meningitis is more common than bacterial, bacterial is more often associated with hearing loss.[74] Bacterial meningitis is also a more serious infection and can be life threatening.

Unilateral Atresia or Microtia

Congenital aural atresia (CAA) or microtia is a birth defect occurring in approximately 1 per 10000 live births as a syndromic or nonsyndromic disorder.[78] CAA phenotypes range from mild symptoms (narrowing of the external auditory canal and hypoplasia of the tympanic membrane and middle ear cavity) to severe symptoms (including the entire absence of the middle ear in combination with anotia, bony atresia of the external auditory canal, and hypoplasia of inner ear structures)[79] and is frequently associated with chromosomal abnormalities, especially deletions on the long arm of chromosome 18 (18q).[80]

Unilateral CAA occurs in approximately 70% of cases and occurs slightly more often in boys than in girls.[81] Surgical remediation of unilateral CAA for purposes of improving the conductive hearing loss is often not recommended at all or, in some cases, is not recommended until adolescence or adulthood. Such surgery is noted to be one of the most difficult otologic surgeries and, on average, results in small improvements in hearing sensitivity.[81,82]

Future Needs

Despite the widespread implementation of newborn hearing screening programs in the United States, systematic etiologic evaluations, especially genetic evaluation and counseling, have not become routine[25]. However, it is clear from a survey of parents of children with hearing loss that they want information about the cause of their child's hearing loss.[83] In fact, etiology of their child's hearing loss is rated as the top question parents have after notification of a hearing loss diagnosis.

Nance[66] has proposed that by screening all newborn infants for just 4 important causes of deafness (DFNB1, CMV, Pendred syndrome, and the mt 12S rRNA A1555G mutation) more than half of all infants with normal hearing at birth who are at high risk for delayed onset hearing loss in infancy would be detected in addition to detecting infants at birth who have the commonest genetic, the commonest

environmental, and the commonest preventable causes of deafness. As demonstrated by this review, that recommended screening protocol is likely to identify numerous cases of permanent UHL and MBHL that would typically not be identified through newborn hearing screening programs that target more severe degrees of hearing loss. As with any screening protocols, the benefits and limitations of such recommendations will require careful consideration before implementation.

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