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REVIEW ARTICLE

Hearing Loss in Children: A Review of Literature

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Childhood hearing loss (HL) can be attributed to both environmental and genetic factors, therefore it can be congenital or acquired in nature. The effect of childhood HL is on language development, literacy, self-esteem, and social skills. Taking into account the negative impact of HL in children, this review article aims to bring into attention of the medical community the different causes of HL in children and the methods of screening and diagnosing HL in children.

Key words: Audiometry, causes of hearing loss, children, infections

INTRODUCTION

Hearing allows one to identify and recognize objects in the world based on the sound he/she produce, hence making communication using sound possible.[1] The process of normal human hearing requires the proper function of the external ear, middle ear, inner ear (cochlea), and ascending brainstem pathways,[2] therefore anything which interferes with the proper functioning of these structures can lead to hearing loss (HL). HL is the most prevailing birth defect, and its prevalence increases as the child reaches adolescence.[3] According to 2018 WHO estimates, children account for 7% (34 million) of all persons living with disabling HL in the world.[4] While the most obvious effect of childhood HL is on language development, it also has an impact on literacy, self-esteem, and social skills, which, in turn, can lead to reduced employment opportunities later in life and psychological consequences that can lead to feelings of isolation, loneliness, and depression.[5,6] Permanent childhood hearing impairment is defined as a confirmed permanent bilateral hearing impairment ≥40 dBHL (hearing level) averaged over the frequencies of 0.5, 1, 2, and 4 kHz in the better hearing ear.[7] It can be attributed to both environmental and genetic factors, therefore it can be congenital or acquired in nature.[3,6] Taking into account the negative impact of HL in children, in the present article, an overview of normal hearing, causes of HL in children, and diagnosis of HL in children have been discussed.

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Overview of normal hearing

The process of normal human hearing is initiated as sound pressure waves travel through the external auditory canal and vibrate the tympanic membrane.[1,2] The ossicular chain in the middle ear space then transmits the acoustic energy to the fluid-filled chambers within the cochlea, consequently imitating electrical and chemical gradients between the endolymph and perilymph, which function to power the cochlea.[2,8] When a sound pressure wave is applied by the stapes to the oval window at the base of the cochlea, a traveling wave is generated that vibrates the basilar membrane maximally at the region tuned to the frequency of the sound stimulus.[2] The vertical movements of the basilar and tectorial membranes generate shearing forces that deflect the hair cell stereo-ciliary bundles in the organ of Corti.[9] Bending of the stereocilia opens mechanosensitive channels near their tips and allows the influx of cations from the endolymph into the hair cell.[2,8] In the inner hair cells, the resultant depolarization triggers synaptic neurotransmission to afferent auditory neurons. In contrast, the outer hair cells generate unique forces

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that modify the physical properties of the organ of Corti and lead to frequency-selective amplification of the inner hair cell response.[10] Bending of the stereocilia opens mechanosensitive channels near their tips, allows the influx of sound information to travel through the auditory nerve to the cochlear nucleus, and follows an organized path along multiple brainstem nuclei, ultimately conveying a signal to the auditory cortex, which lies within the temporal lobe adjacent to the Sylvian fissure.[2]

Classification of hearing loss

There are three basic types of HL: conductive HL (CHL), sensorineural HL (SNHL), and mixed HL respectively basing on which part of the auditory system is affected.[11,12] CHL occurs when sound is not conducted efficiently through the external ear canal to the middle ear. Whereas, SNHL occurs when there is damage to the inner ear or to the nerve pathways from the inner ear to the brain. Anything that disrupts sound getting to the cochlea can be considered CHL, and loss at the point of the cochlea or proximal to the cochlea is considered SNHL.[13,14] Mixed HL is defined as CHL and SNHL.[11] While the SNHL is far more common in adults, CHL accounts for 90%–95% of all childhood HL.[12,15]

HLs may be classified according to laterality, symmetry, clinical characteristic (syndromic or not), time of onset (congenital, perinatal, or postnatal), hereditary (genetic or not), time of manifestation (prelingual, perilingual, or post-lingual), and intensity (mild, moderate, severe, and profound).[14]

Causes of hearing loss in children

Hereditary and environmental factors are involved in the etiology of pediatric HL. More than forty genes are associated with the inheritance of HL, among which involves mutations in the gap junction protein beta 2 gene (GJB2) gene. Among environmental factors, viral infection is thought to play a major role in HL.[16] The causes of HL can be broadly grouped into congenital and acquired, such as infections, traumatic, autoimmune, and neoplastic, to name a few [Figure 1].

Congenital

Congenital HL (hearing loss present at birth) occurs when the ability of the ear to convert the vibratory mechanical energy of sound into the electrical energy of nerve impulses is impaired.[11] Congenital hearing impairment affects nearly 1 in every 1000 live births; it is one of the most distressing disorders and the most frequent birth defect in developed societies.[5] In the majority of hearing-impaired children, HL is due to genetic factors, most often a single-gene defect.[11] These defects can have different modes of inheritance and different prevalence. HL is classified to reflect the presence (syndromic HL) or absence (nonsyndromic) of coinherited physical or laboratory findings.[11] Autosomal recessive nonsyndromic HL accounts for 80% of genetic cases and is often congenital, whereas approximately 20% of nonsyndromic HL is inherited as autosomal dominant and is usually of delayed onset.[5,11] Although the frequency of causative genes varies across different populations and ethnicities, the most frequent genetic cause of severe-to-profound autosomal recessive nonsyndromic HL is mutation in the GJB2;[11,16] other genes that are common causes of HL include GJB6, SLC26A4, and OTOF.[5]

Other congenital causes of HL include malformations of the middle ear which can range from the altered configuration and size of the tympanic cavity to variation in the number, size, and configuration of ossicles. Anomalies of the round window and, more rarely, of the oval window may still occur.[17] The most common malformation is isolated ossicular deformity involving the stapes superstructure and the long apophysis of the incus, and the most common congenital ossicular fixation is stapes fixation, also known as otosclerosis.[18] Raveh *et al.*[19] presented the results of exploratory tympanotomy performed at a large pediatrics otolaryngology center in patients with nonserous congenital CHL, and they found that 42 children had malformation of one or more ossicles without fixation of the stapes and 19 children had fixed stapes. Other congenital malformations of the middle ear that can cause HL have been summarized by Teunissen and Cremers[20] basing on the surgical approach, dividing them into the following four main groups: isolated stapes ankylosis, stapes ankylosis associated with other ossicular malformations, deformity of the ossicular chain with mobile stapes footplate, and severe aplasia or dysplasia of oval or round windows.

Dysplasias have been attributed to be among the causes of HL in children. In one of the largest studies of hearing health in skeletal dysplasia patients, Tunkel *et al*.[21] found HL in over one-fourth of children with skeletal dysplasias. Children with skeletal dysplasias were more likely to have abnormal tympanometry, reflecting the greater likelihood of middle ear disease. Another dysplastic condition is Mondini dysplasia, an inner ear abnormality characterized by the development of an incomplete cochlea due to helical cavitation of otic mesenchyme.[22] It is thought to be due to the arrest of neural tube development during the 7th week of gestational age.[23] Arellano *et al.*[22] reported on a series of cases with HL secondary to Mondini dysplasia. Similarly, Lin *et al*.[23] reported HL in a 10-month-old girl with Mondini dysplasia.

Infections

When an organism's body is invaded by a disease-causing microorganism, it ultimately responds to such invasion, and this is termed as an infection. Infection may be caused by viruses, bacteria, fungi, and/or parasites. There is a

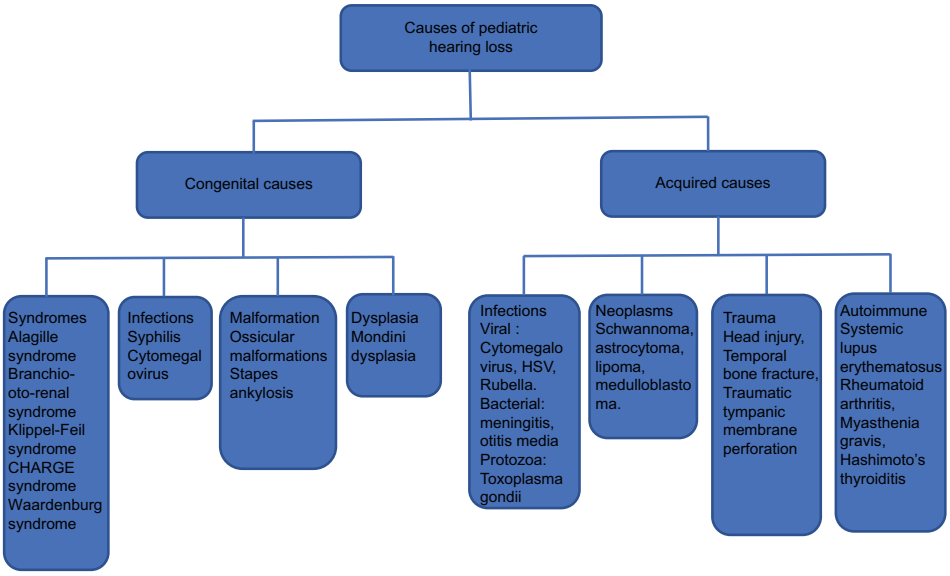

Figure 1: Some of the causes of hearing loss in children

well-established association between some congenital infections and HL.[2,24-26] The most frequent infectious agents associated with HL are *Cytomegalovirus* (CMV), rubella virus, *Toxoplasma gondii,* and the herpes virus and of recent, HIV has also been included in this risk group.[14] HIV infection can lead to CHL through bacterial and fungal infections, secondary to immunosuppression.[27]

Bacterial meningitis, particularly from *Streptococcus pneumoniae*, has been reported to be one of the most common postnatal causes of HL in children.[24,28] Meningogenic labyrinthitis is most frequently due to bacterial meningitis and is usually bilateral. The offending pathogens are believed to invade the membranous labyrinth through the cochlear aqueducts or the lamina cribrosa of the vestibule, resulting in suppurative labyrinthitis, where the organisms gain access into the inner ear through the round window, the oval window, or via an anomalous connection between the middle and inner ear. In a study from Pakistan,[29] the frequency of HL was found to be at 22% following an episode of acute bacterial meningitis. A study from England by Fortnum and Davis[30] indicated that 7.4% of the children who had suffered bacterial meningitis had some degree of SNHL or mixed HL as a direct consequence of the disease. The impairments ranged from mild unilateral to profound bilateral and the affected children were aged between 0 (i.e., infection at birth) and 15 years, and hence, they concluded that bacterial meningitis of any type can result in sensorineural hearing impairment of any degree in a child of any age. In another study, Richardson *et al.*[24] concluded that SNHL developed during the earliest stages of meningitis. Permanent deafness was rare, but 10% of the patients had a rapidly reversible cochlear dysfunction which may have progressed to permanent deafness if the patients had not been treated promptly.

Congenital syphilis (CS), a condition caused by transplacental transmission of *Treponema pallidum,* is initially characterized by meningoneuritis and labyrinthitis and progresses to interstitial keratitis, SNHL, and peg teeth (Hutchinson's triad).[31] Eight-nerve deafness occurs in about 3% of CS cases and is secondary to luetic involvement of the temporal bone. Eight-nerve involvement can be unilateral or bilateral, and it often occurs in the first decade of life.[32,33] Pessoa and Galvão[34] reported on the case of HL in a 7-year-old girl who was diagnosed with CS when she was 2 years old. In another case report, Marfatia *et al.*[33] reported HL in a 14-year-old girl.

Of the viral infections that are linked with HL, CMV infection has been extensively studied. CMV infection is omnipresent in the general population and rarely produces symptoms in the immunocompetent infant, child, or adult. CMV-induced illness may, in contrast, be serious in individuals with impaired immune systems, including HIV-infected individuals, solid organ and hematopoietic transplant patients, and infants infected *in utero*.[35] CMV infection has an estimated overall birth prevalence of approximately 0.3%–2.4% and approximately 10% of infected infants are born with the clinical symptoms of congenital CMV infection.[36,37] HL associated with symptomatic CMV infection is often progressive in about 50% of patients and ultimately becomes severe to profound in the affected ear in 78% of patients.[36] The association between congenital CMV infection and HL, especially SNHL,

has been known for decades, although the mechanism by which the virus causes hearing impairment in some children and not others is still not fully understood.[38] Furutate *et al*.[37] collected preserved dried umbilical cords from 134 children with bilateral (46 children) or unilateral (88 children) SNHL and extracted CMV DNA which was detected by quantitative polymerase chain reaction. They found that CMV DNA from the dried umbilical cords was detected in 8.7% of the bilateral SNHL and 9.1% of unilateral SNHL. In another study, Fowler and Boppana[38] established that congenital CMV infection significantly contributes to SNHL in many infant populations. Although most children with congenital CMV infection do not develop HL, it is difficult to predict which children with congenital CMV infection will develop HL and among those who do develop loss, whether or not the loss will continue to deteriorate. Similarly, a retrospective analysis of the etiology of SNHL by Ogawa *et al.*[16] demonstrated that congenital CMV infection is responsible for a substantial proportion of early-childhood SNHL.

Herpes simplex virus (HSV) exposure is often quoted as a risk factor for the development of SNHL in a newborn child.[39] HSVs are large, enveloped viruses containing DNA and are of two major types. Type 1 (HSV) usually involves the face and skin above the waist. Type 2 (HSV) usually involves the genitalia and skin below the waist in adults.[40] Reports of seroconversion of HSV antibody titers in idiopathic sudden SNHL and the finding of HSV-specific DNA in human spiral and vestibular ganglia of asymptomatic individuals support the role of herpes viruses in the pathogenesis of HL.[41] HSV is most frequently transmitted to an infant during passage through an infected maternal lower genital tract during birth.[40] In their study, Al Muhaimeed and Zakzouk[40] reported that 46 of the 82 infected children (56%) with HSV were found to have bilateral SNHL. According to Cohen *et al.,*[27] the degree of HL caused by viruses varies depending on the type of virus. CMV causes severe HL, Rubella virus causes mild-to-moderate HL, and HSV causes moderate-to-profound HL.

HL has been reported in about 20% of the congenital toxoplasmosis cases, especially in untreated children or those treated for a very short period.[14] Toxoplasmosis is a systemic infection caused by the protozoan parasite *T. gondii*, and congenital toxoplasmosis is caused by vertical transmission from the mother to the fetus.[42] Salviz *et al.*[43] postulated that the possible pathophysiology of the HL in congenital toxoplasmosis is due to postnatal inflammatory response to the tachyzoite form of *T. gondii* found in the internal auditory canal and in the temporal bone, specifically in the spiral ligament, the stria vascularis, and the saccular macula or the internal auditory canal. In a study from Brazil, it was observed that congenital toxoplasmosis was a risk factor for HL.[14] On the contrary, Austeng *et al.*[44] found no association between maternal *T. gondii* infection in pregnancy and subsequent HL in the offspring. Hence, they concluded that *T. gondii* infection in pregnancy was not an important cause of childhood HL. In addition, in another study by Leite Filho *et al.*,[45] it was observed that children exposed to toxoplasmosis during pregnancy did not differ from nonexposed children in relation to the occurrence of HL.

A spectrum of inflammatory disorders affects the middle ear cavity, with acute otitis media and otitis media with effusion (OME) being the most prevalent in children.[46,47] Otitis media has multifactorial etiological factors including adenoids hypertrophy, infection (viral or bacteria), allergy, and environmental and social factors.[47] OME frequently leads to CHL as a result of reduced air pressure in the middle ear, fluid retained in the middle ear cavity, increased stiffness and mass of the tympanum, pathological changes in the tympanic membrane or ossicles such as destruction of the ossicles, or fibrosis and cholesteatoma in the middle ear.[48-50] Abdullah *et al.*[47] assessed fifty ears of children who had otitis media and found that 24 ears had moderate CHL, 16 ears had mild HL, while 4 ears had severe HL. In a study that was carried out among Saudi preschoolchildren,[51] acute OME was the major cause of deafness, followed by chronic otitis media. Anggraeni *et al.*[50] investigated on otitis media-associated HL in schoolchildren in Indonesia and found that otitis media contributed to 57% of mild-to-moderate HL cases and 79% of bilateral HL.

Trauma

Of the several etiologies of HL in children, head trauma is cited to be among the acquired causes, regardless of its severity.[52,53] Damage to the peripheral and/or central auditory pathways can occur as a primary or secondary insult after closed head injury. Primary audiological deficits after a head injury can appear as a result of direct trauma to the middle and inner ear (e.g., in fractures of the base of the skull) or due to rupture or tearing of central neuronal pathways.[53] Early secondary impairment can result from raised intracranial pressure due to bleeding and hematoma and later in the course because of diffuse axonal degeneration.[53,54] Experimental studies have shown electrophysiological and histopathological changes in the inner ear following head injury, and the postmortem histopathologic studies following head injury revealed changes in the internal auditory canal, the tissues of the inner ear, the vestibulocochlear nerve, and the brainstem.[54]

Temporal bone fractures constitute a significant bulk of basilar skull fractures, which, in turn, constitute the most common skull fractures following head injury,[55] and fracture of the temporal bone can cause SNHL and/or CHL.[12] Up to

82% of children with temporal bone fractures have HL at presentation; of these cases, 67% will be CHL, 21% will be SNHL, and 12% will be mixed.[28] Zimmerman *et al.*[56] studied fifty children who had sustained head injuries and found that the incidence of CHL was 32% against 16% for SNHL. Cockrell and Gregory[57] performed audiological evaluation in 62 children who had suffered from traumatic brain injuries and found that 16% of the children had CHL, 13% had SNHL, and 16% had central auditory processing problems.

Perforation of the tympanic membrane following trauma is another cause of HL. In their study, Olowookere *et al.*[58] found that trauma to the ear accounted for only 3% of the cases of tympanic membrane perforation. Tympanic membrane perforation reduces the total ratio of the surface area, allowing the sound waves to directly pass through the middle ear.[59] Tympanic membrane perforation leads to a varying degree of CHL[60] and the size of perforation may define the severity of HL.[59] Traumatic membrane perforation can be due to direct trauma, acoustic trauma, barotrauma, and iatrogenic causes[60,61] such as unskilled instrumentation or syringing of the ear, sudden air compression as in boxing, hand-slap, and blasts.[58] Another sequela of trauma can be rupture of the round or oval window membranes.[12]

Neoplasms

Neoplasms/tumors can cause HL through one or more of the following mechanisms: direct compression of the cochlear nerve by the tumor; occlusion or vascular compression of the internal auditory artery; intratumor bleeding; internal auditory canal occlusion; and toxic substance produced by the tumor that causes degeneration of the inner ear.[62,63] These tumors include schwannomas[64,65] and tumors of neuroepithelial origin such as pylocytic astrocytomas (PAs) and medulloblastomas (MBs).[63,66,67] Schwannomas represent 0.8% of all childhood tumors and 2.08% of all unilateral acoustic neuromas, and occasionally, early deafness in childhood due to schwannoma may pass unnoticed because it often causes unilateral HL.[68] Some authors have described that vestibular schwannomas can present with HL, particularly in individuals with neurofibromatosis type 2.[28] HL secondary to schwannoma has been reported by Thomas *et al.*[64] and Massinger *et al*.[69] in a 10-year-old boy and 12-year-old girl, respectively.

PA accounts for 5%–10% of all gliomas and is the second most common pediatric brain tumor.[63,66] Although rarely do PA cause HL, these tumors can produce changes in the blood supply to the auditory nerve, destroy cochlear nerve fibers, and disturb the inner ear fluids with biochemical changes, all of which can result in a HL.[63] These tumors commonly occur around the third and fourth ventricles, in optic chiasm and hypothalamus, however cases in which PA arise from the VIII nerve complex have been reported by Mirone *et al*.[66] On the other hand, Schneider *et al*.[67] reported a case of PA in the left cerebellopontine angle that caused HL due to stretching or compression of the auditory nerve and mechanical stress on the nerve blood supply.

Another neoplastic condition that is attributed to cause HL in children is MB. MB is said to be a highly malignant neuroepithelial tumor of the posterior fossa that accounts for 10% of all intracranial neoplasms and 29% of all pediatric fossa tumors in children.[70] HL because of MB in children has been well documented in literature.[70,71] Other tumors that have been documented to be the cause of HL in children, though rare, include middle ear lipomas,[72,73] middle ear lymphoma,[74] congenital cholesteatoma,[75] and aneurysmal bone cyst of the temporal bone.[76]

Autoimmune

McCabe had proposed the existence of autoimmune SNHL (ASNHL) about 40 years ago, and ever since, evidence has confirmed the existence of autoimmune-mediated inner ear disease (AIED), a potentially treatable cause of SNHL.[77,78] ASNHL is characterized by bilateral disease, often with the severity of HL being asymmetric.[79] AIED is defined as primary when the pathology is restricted to the ear, however, in up to a third of cases, AIED occurs in the context of systemic autoimmune disease and is defined as secondary.[80] Some of the identified autoimmune diseases affecting hearing include systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, ASNHL, and Hashimoto's thyroiditis.[81]

For many years, it has been known that the inner ear communicates with the systemic immune system and can rapidly mount an immune response against pathogens and foreign proteins to which it has been sensitized.[82] Although the inner ear is believed to be an immune-privileged site protected by the blood–labyrinthine barrier, cochlear innate immunity has been proposed to contribute to the initiation of an adaptive immune response in the cochlea by promoting a response to antigen challenge.[81,83] A number of inner ear antigens have been proposed as targets of antibodies due to an autoimmune response, including type 2 and type 9 collagen, beta-actin, cochlin, and beta-tectorin.[84] Baek *et al.*[85] attributed the etiopathogenesis of ASNHL to the cochlin-specific interferon gamma (IFN-γ)-producing T-cells. Cochlin is among the most abundant protein of the inner ear, thus it serves as a prominent candidate antigen for targeting inner ear inflammation and autoimmune-mediated HL. Baek *et al.*[85] found that cochlin autoreactivity was significantly enhanced in patients with ASNHL. This cochlin responsiveness involves IFN-γ-producing $CD4^+$ and $CD8^+$ T cells as well as elevated cochlin-specific serum antibodies. In another study, Nair

et al.[86] reported on antibodies against choline transporter-like protein 2 (CTL2), an inner ear glycoprotein. They described that sensory cells die after binding of an antibody to CTL2 molecules. Their postulation was that antibody acts by blocking the transporter function of the molecule either by blocking the substrate receptor of the carbohydrate or by causing steric hindrance in the transporter pore and in either case, leads to antibody-mediated HL.

Although autoimmune inner ear disease most commonly affects people in the third to sixth decades of life,[80] cases of autoimmune-mediated HL in children have been well documented in literature. Huang and Sataloff[77] reported cases of seven children with HL secondary to AIED, and Marsili *et al*.[87] reported a case of HL in a 15-year-old boy diagnosed with AIED.

Ototoxic medications and substances

Ototoxicity has been described as a functional impairment and cellular degeneration of the tissues of the inner ear caused by therapeutic agents.[88] The hearing impairment in children caused by ototoxic drugs is usually bilateral, is symmetric, and of variable severity.[25] Some of the identified ototoxic drugs include aminoglycoside antibiotics, platinum-based chemotherapeutic agents (cisplatin and carboplatin), loop diuretics, macrolide antibiotics, and antimalarials.[88,89]

Children may be exposed to ototoxic drugs/substances prenatally or postnatally. It has been well documented in literature that ingestion of ototoxic drugs/substances by pregnant women can result in HL in the offspring.[90-92] The period of gestation when the use of ototoxic medications/substances is most likely to cause damage to the auditory system is in the first trimester, especially in the 6th and 7th weeks.[25] Among these substances is alcohol. Alcohol by itself is a toxin to the fetus, as is its major metabolite, acetaldehyde. Alcohol can cause a direct effect on cells and can also cause damage due to hypoxia and disturbances in prostaglandin physiology.[90] For example, a meta-analysis aimed at identifying the comorbid conditions that co-occur in individuals with fetal alcohol syndrome Disorder, deduced that the pooled prevalence of SNHL and CHL was estimated to be up to 129 times higher in individuals with FAS than the prevalence of moderate-to-severe HL in the general population.[93]

The use of ototoxic drugs during pregnancy may as well lead to HL in children. In one case report, severe bilateral perceptive HL in a neonate was diagnosed, after the mother was treated for cervical cancer with cisplatin and paclitaxel from 26th to 34th weeks of pregnancy.[94] In a case–control study that evaluated the risk of HL in children due to *in utero* exposure to drugs, it was observed that HL was associated with valproic acid and low-dose acetylsalicylic acid exposure during pregnancy.[95] Aminoglycosides are said to cross the blood–placenta barrier, and animal studies have shown them to cause HL in children. Czeizel *et al*.[91] studied the teratological effect of aminoglycoside antibiotic treatment during pregnancy and concluded that the risk of deafness in children cannot be excluded, but the magnitude is estimated to be small.

Postnatally, treatment-induced HL has been documented. Many therapeutics can be classified as "ototoxic," despite that, such drugs remain in current use, either because the risk of damage to the ear is small, or because there simply are no comparable alternatives.[96] Aminoglycosides are among the most commonly used antibiotics for empirical treatment of neonatal sepsis or to treat febrile neutropenia or Gram-negative infections; however, their ototoxicity depends on the total dose administered, the duration of treatment, as well as serum concentrations.[97,98] Although they are dose dependent, there is no clear dose or duration threshold at which the risk of HL increases significantly, as some children do not develop noticeable HL. Despite high exposure to aminoglycosides, there are also reports of irreversible, profound HL after very low exposures.[97]

Platinum-based chemotherapeutical agents are important alkylating agents that are effective in the management of childhood cancers.[99] Unfortunately, these drugs commonly cause SNHL that is progressive, bilateral, and irreversible.[100] The incidence of HL in patients receiving platinum-based chemotherapy varies widely in the literature.[101] Bertolini *et al*.[102] observed that deterioration of hearing of Grade 2 or above was in 37% of children treated with cisplatin and 43% of patients treated with cisplatin plus carboplatin, and had concluded that carboplatin, at a standard dose, does not appear to be a significant risk factor for ototoxicity even in patients who have already been treated with cisplatin. Cisplatin which works by the disruption of DNA replication and repair can cross the blood–labyrinth barrier to gain access to cochlear tissues.[100] Subsequently, it generates reactive oxygen species that induce mitochondrial damage, and apoptosis of the cochlear outer hair cells depletes natural antioxidants such as glutathione and damages the stria vascularis and reparative stem cells of the inner ear.[100,103]

Other causes

There are several other causes of HL in children. Hospitalization for more than 5 days in neonatal intensive care unit is reported to increase HL incidence by about 5–10 times if compared with that in the general newborn population.[104,105] In addition, several syndromes have been described to be associated with inner ear malformation.[28] A study by Mehta *et al*.[106] reported that of the individuals with syndromic

manifestations, Usher and Waardenburg syndromes were most commonly observed.

Diagnosing hearing loss in children

The diagnosis of HL in children may be done at any stage of their development, and the type may be dictated by the cause of HL. In newborns and infants, HL can be screened using different methods. For diagnostic purposes, there are several investigations that can be carried out such as audiometry, genetic tests, imaging studies, otoscopy, and tympanometry.

Screening newborns and infants for hearing loss

Accurate diagnosis of HL in infants is challenging, and an attempt of doing so had led to the establishment of the Universal Newborn Hearing Screening and Intervention (UNHSI) program, which has been widely adopted throughout North America, Europe, and in most other developed regions, primarily as a result of technological advances in screening and intervention modalities.[107] In the UNHSI program, diagnosis of hearing disorders in newborns and infants is generally a two-stage process that entails measuring otoacoustic emissions (OAE) or performing automated auditory brainstem response (A-ABR) audiometry, or both.[108] OAEs are forms of energy, measured as sound, generated by the outer hair cells of the human cochlea, in response to received auditory input, while A-ABR test records brainstem electrical activity in response to sounds presented to the infant via earphones.[107]

In two-stage screening, OAE measurement is followed by A-ABR audiometry.[108] In this system, if an infant passes the OAE, no additional testing is done, but when fails the OAE, he/she is next screened with A-ABR. Infants who fail the A-ABR screening are referred for diagnostic testing to determine whether they have permanent HL (PHL) or not.[109] A weakness of OAE measurement is that it does not detect fluctuating hearing impairments or those due to auditory neuropathy.[108] Wolff *et al*.[110] did a systematic review of the literature to assess the accuracy, effectiveness, and effects of interventions after screening and found that eight diagnostic studies comparing OAE with ABR showed sensitivity which varied between 50% and 100% and the specificity from 49.1% to 97.2%. In another study, Johnson *et al*.[109] concluded that if all infants were screened for HL using the two-stage OAE/A-ABR system, then approximately 23% of those with PHL at approximately 9 months of age would have passed the A-ABR. Despite some limitations of this screening program, there is strong evidence indicating that two-step screening is highly effective in identifying infants with HL.[107]

Genetic tests

Genetic screening is defined as the analysis of human DNA in order to detect heritable-related mutations.[111] The advancements in the molecular genetics of hearing impairment have demonstrated that more than 50% of children with SNHL have attributable genetic factors, thus genetic testing may be considered to be a powerful tool for addressing hearing impairment in children.[5,112] Abnormalities in many different single genes or gene pairs can cause deafness, with some studies reporting that defects in a single gene, called GJB2, encode for connexin 26 being responsible for more than half of the genetic causes of HL.[113,114] Mutations in the gene coding for connexin 26, account for about half of the autosomal recessive cases, therefore particularly important as a cause of genetic childhood HL.[114] Establishing the etiology of HL through genetic testing eliminates further expenditure in diagnostic health-care costs and also it provides invaluable information that can guide medical management and intervention of babies with HL.[115] Regarding the genetic testing, it is recommended that it may be guided by the case history, phenotype, physical examination, audiometry, and the relative prevalence of a gene in a clinical population.[113,116]

Imaging studies

Computed tomography (CT) and magnetic resonance imaging (MRI) have become an essential part of the evaluation of pediatric SNHL, with anomalies being found in up to 40% of patients, ranging from major anatomic abnormalities to subtle dysplasia.[117] These imaging modalities are helpful in identifying the potential etiology for HL, to define the anatomy of the temporal bone and the central auditory pathway, to identify abnormalities that may predict HL progression or prognosis, and to identify additional intracranial abnormalities that may require further workup and/or intervention.[118] Regarding which imaging modality is best, some physicians are proponents of MRI over CT, while others note that CT may be superior yet, some other both. Other clinicians decide according to age, severity, or laterality of a given patient's presentation. However, better understanding of the relative and diagnosis-specific potential yields of each imaging modality allows sophistication with which these images may be ordered.[119]

Audiometry

Audiometry, which is performed using an audiometer, is the science of measuring hearing acuity and variations in a sound and is considered to be a comprehensive baseline ear health screening tool.[120,121] There are several techniques of performing audiometry, including pure tone audiometry (PTA), speech audiometry, visual reinforcement audiometry (VRA), and play audiometry (PA).

The PTA assesses the type (CHL, SNHL, and mixed) and degree of HL.[53,120] PTA consists of air-conduction and bone-conduction tests. The entire range of human hearing is from 20 to 20,000 Hz. Air-conduction hearing thresholds are measured for tonal stimuli at the range of frequencies from 0.125 to 8 kHz with the use of headphones and the patient gets a pure tone of one frequency. Then, bone-conduction hearing thresholds are measured for tonal stimuli at the range of frequencies from 0.25 to 4 kHz, with the use of a headband with oscillator.[120,122] In the CHL, air-conduction thresholds worsen, so the air-conduction curve is shifted down, whereas bone-conduction thresholds remain unchanged.[122] According to the International Classification of HL, to calculate the degree of HL, it is necessary to summarize the four values, i.e., the lowest audible sound intensity using the frequencies of 500, 1000, 2000, and 4000 Hz, and then to divide the sum by 4 to get the arithmetic average.[120]

Speech audiometry assesses auditory discrimination as opposed to auditory acuity, requiring the individual to repeat standard word lists delivered through headphones at varying intensities, which, therefore, provides information on word recognition and about discomfort or tolerance to speech stimuli.[53,123,124] Speech audiometry is performed to obtain the speech recognition (reception) threshold (SRT) or speech detection (awareness) thresholds (SDTs) using spondee words and supra-threshold speech recognition. The SRT measures the lowest dBHL at which 50% of the time spondee can be correctly repeated or identified, whereas, SDT assesses the lowest dBHL at which the presence of speech can be correctly detected.[125] It is recommended to rule out ear diseases if unilateral or asymmetrically poor speech discrimination scores (a difference >15% between ears) or a bilateral speech discrimination scores of < 80% are observed.[125] The setback of speech audiometry lies in that there are certain measures that can be affected by language differences; thus, an individual's ability to hear discriminating differences and repeat certain words can be affected.[126]

VRA is routinely used to evaluate hearing in infants and children aged 6 months to 2 years.[127] It capitalizes on a child's natural instinct to respond to auditory stimuli by turning toward the stimuli.[128] A limitation of VRA is that the head turn response can extinguish or habituate before a full hearing assessment can be completed as it is an operant-conditioned response. That is, the desired behavior is rewarded, thus increasing the likelihood that the behavior will continue.[127,128]

Treatment of hearing loss in children

The management of children who have HL requires a multidisciplinary team-based approach and should encompass counseling of the parents as well. The overall objectives of management are to minimize the effect that the HL will have on speech and language development and to provide appropriate strategies for communication.[13] The initial approach of managing HL should be to treat the underlying etiology. The treatment modalities of HL may be medical (antimicrobial therapies and anti-inflammatory therapies), surgical treatment (e.g., tumor excision and stapedectomy), and amplification of sound.[129]

Medical treatment entails the use of steroids, antivirals, and antibiotics. In a study by Övet *et al.,*[130] it was reported that significant hearing improvement may be obtained with the use of systemic steroids alone in pediatric patients with sudden SNHL. Antivirals have been used in cases of HL caused by viral infection. Ganciclovir (administered intravenously) is the treatment for both early and delayed SNHL resulting from congenital CMV infection. It prevents SNHL progression and sometimes can improve hearing status.[27] Acyclovir has been used to treat HL caused by HSV-1.[27,41]

In the cases of HL during bacterial meningitis, parental penicillin has been shown to be effective.[24] In cases of otitis media in children, antibiotics should be considered if symptoms persist or do not improve within 4 days, or in those younger than 2 years with bilateral acute otitis media, or who have a tympanic membrane perforation.[131]

The surgical treatment of HL can be grouped into reparative procedures (in case of managing infectious or traumatic causes) and restorative procedures if HL cannot be treated with conventional amplification.[129] Surgical treatment is considered to be beneficial in cases where there is an air–bone gap that is amenable to correction by surgical intervention.[11]

Restoration of hearing is achieved by using hearing devices which are either implantable or nonimplantable. These devices include conventional air-conduction hearing aids, bone-anchored hearing aids (BAHAs), and cochlear implants.[11,132] The conventional air-conduction hearing aids are incorporated with a microphone that converts sounds into electrical signals, returned to the ear as amplified sound. They are useful for patients with mild-to-severe HL.[132]

BAHA devices incorporate a titanium plate that is surgically anchored to the skull on the hearing-impaired side, to directly stimulate the inner ear by conducting sound vibrations through the bone.[132] Some of the indications for BAHA include severe CHL, congenital ear canal atresia, SNHL, and difficulty wearing a conventional air-conduction aid with an ear mold, due to recurrent ear infections.[132,133]

The cochlear implant is a biomedical device that is surgically placed into the cochlea. It converts sound to an electrical signal, which is then conducted to the spiral ganglion cells in the cochlea via electrodes.[134] This conduction ultimately produces an auditory sensation to the individual that allows the detection of sounds, especially speech sounds.[135]

CONCLUSION

HL in children is among the most prevalent health-related issue globally. There is a vast array of etiological factors of HL in children. HL in children affects both the child and his/her parents/caretakers. The effect on the child is in terms of speech and language development, communication, literacy, and learning, whereas, the parents/caretakers usually are often at greater risk of stress and have increased cost in terms of seeking for their children's well-being. It is the duty of a physician to take a thorough history of the children who present with HL, followed by ordering appropriate investigations to establish the cause of HL. The management of children who have HL requires a multidisciplinary team-based approach and should encompass counseling of the parents as well.

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Conflicts of interest

There are no conflicts of interest.

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