VILNIUS UNIVERSITY

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The Final thesis

Congenital hearing loss causes and workup

Anton Chertin, VI-year, 1 group

Institute of Clinical Medicine, Clinic of Ear Nose and Throat and Eye diseases

Supervisor: Lecturer Arnoldas Morozas

The head of clinic: Prof. dr. Eugenijus Lesinskas

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Email of the student: anton.chertin@mf.stud.vu.lt

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List of abbreviations:

1. SNHL- Sensorineural hearing loss
2. CSNHL- Congenital sensorineural hearing loss
3. CDC- Center of disease control
4. USH- Usher syndrome
5. ARAS- Autosomal recessive Alport syndrome
6. WS- Waardenburg syndrome
7. TCS- Treacher-Collins syndrome
8. BORS- Branchio-oto-renal syndrome
9. CRS- Congenital rubella syndrome
10. Cx26- Connexin 26
11. GJB2- Gap Junction Protein Beta 2
12. NSHL- Non syndromic hearing loss
13. OAE- Otoacoustic emissions
14. AABR- Automated auditory brainstem response
15. BTE- Behind the ear
16. CI- Cochlear implant

1. Summary

Congenital hearing loss is a prevalent condition among pediatric patients. This condition has various etiologies, which can be genetic, environmental, or infectious that may lead to different types of hearing loss that vary in severity and clinical outcome. According to the etiological factor and severity, the immediate therapeutic decision is made and guide prevention and counseling. Management options include hearing aids, surgical treatment, and speech therapies. This work explores the importance of early screening and intervention of congenital hearing loss and its impact on a child's prosperity and outcome.

2. Keywords

Congenital hearing loss, the ear, genetic syndromes, CMV, screening programs, cochlear implants

3. Introduction

Congenital hearing loss is a prevalent condition among the pediatric population, and it occurs in 1 to 3 in every 1000 live births affected by this condition, as the Centers for Disease Control and Prevention (CDC) reported. (1) The condition may exhibit a spectrum of severity, ranging from mild to severe, with potential unilateral or bilateral involvement and impacting diverse regions within the auditory system. The etiological factors of congenital hearing loss include genetic causes, infections, craniofacial malformations, and environmental factors. (2) Hearing loss in children could impact normal development and daily life activities such as language and communication skills and generally may seriously affect the quality of life. It could also interfere with a child's school achievements and social development. Early detection is essential as it could minimize the impact on proper development and complications. With appropriate interventions such as speech therapy, hearing aids, cochlear implants (CI), and speech therapy, including the teaching of sign language to ensure a better quality of life and the possibility for the child to communicate with the community, make better social interactions, join the workforce and reach their full potential.

Optimal approaches for diagnosing and effectively managing congenital hearing loss require a multidisciplinary approach involving various healthcare professionals, including audiologists, speech therapists, geneticists, and pediatricians. (2) Many developed countries have implemented neonatal hearing screening programs to detect congenital hearing loss in

newborns aiming to test all infants within the first month of their birth, leading to significantly improved outcomes for children with hearing loss (2).

The thesis aims to study the causes and workup of congenital hearing loss with particular attention to recent advancements in the field regarding the significance of early intervention, and it actively discusses the implementation of screening programs, emphasizing their impact on patient outcomes.

4. Ear anatomy

The human ear is a complex organ responsible for both hearing and equilibrium by the transduction of sounds to electrical nerve impulses, which ultimately stimulates the auditory cortex and allows us to perceive the sounds around us. The vestibular system maintains equilibrium by detecting head position and movement. To have more insight into the pathological background of congenital hearing loss, familiarity with the typical anatomy of the ear is crucial. The ear is categorized into three distinct sections: the outer ear, the middle ear, and the inner ear. The outer ear includes the auricle, which is the visible part of the ear and is made of elastic cartilage.(2)

The external auditory canal encloses the external tympanic membrane and contains glands that produce cerumen, protecting the tympanic membrane from foreign bodies or insects that could potentially damage it. The middle ear is located medially to the tympanic membrane (eardrum). It can be visualized as a rectangular box housing the tympanic cavity, an air-filled space, and the ossicles: the malleus, incus, and stapes. Upon the eardrum's movement, the ossicles create a movement called oscillation, which transmit sound waves to the oval window and eventually to the inner. (3) The eustachian tube connects the middle ear to the nasopharynx and regulates the pressure within the middle ear, helping to prevent damage to the delicate structures within it. The two primary components of the inner ear are the cochlea and vestibule. Their roles are to facilitate hearing and maintain balance. The bony labyrinth forms the outer part of the inner ear, filled with perilymph, while the membranous labyrinth, filled with endolymph, constitutes its inner part. (2) The labyrinth makes up all parts of the inner ear. The vestibular system, accountable for maintaining balance and spatial orientation, includes the otolith organs such as the utricle, which detects horizontal movements, and the saccule, which detects sagittal movements and changes in static equilibrium. Additionally, the semicircular canals, consisting of the anterior, posterior, and lateral canals positioned at 90-degree angles from each other, detect head rotation and influence dynamic equilibrium The labyrinth makes up all parts of the

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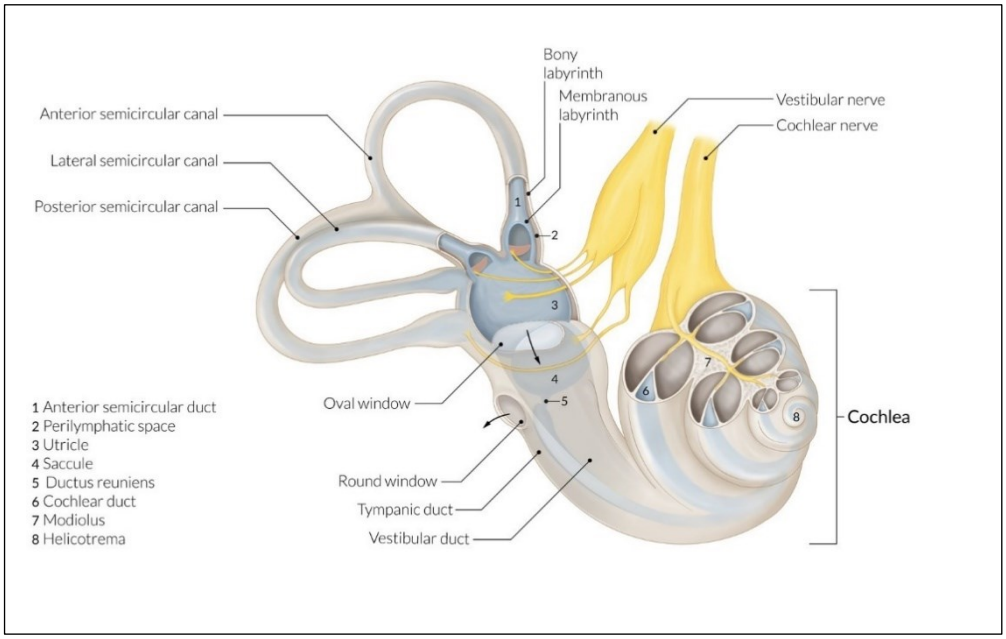

Figure 1- the inner ear (4)

The cochlea, a snail-spiral-shaped structure, serves a crucial function in the sense of hearing by contributing to the process of auditory transduction.

Its shape allows stimulation of various areas of the spiral by differing frequencies. The cochlea is structured with three chambers filled with fluid: scala vestibuli, which is connected to the middle ear by the oval window, scala media which houses the organ of Corti and scala tympani, which is connected to the middle ear by the round window. The Organ of Corti is supported by the basilar membrane and situated in the scala media, and scala tympani plays a vital role in hearing. It comprises one row of inner hair cells and three rows of outer hair cells. When sound waves pass through the cochlea, they cause the stereocilia on the hair cells to move, which is facilitated by an electromechanical force and is then transmitted to the central nervous system via the auditory nerve to facilitate audition. (3)

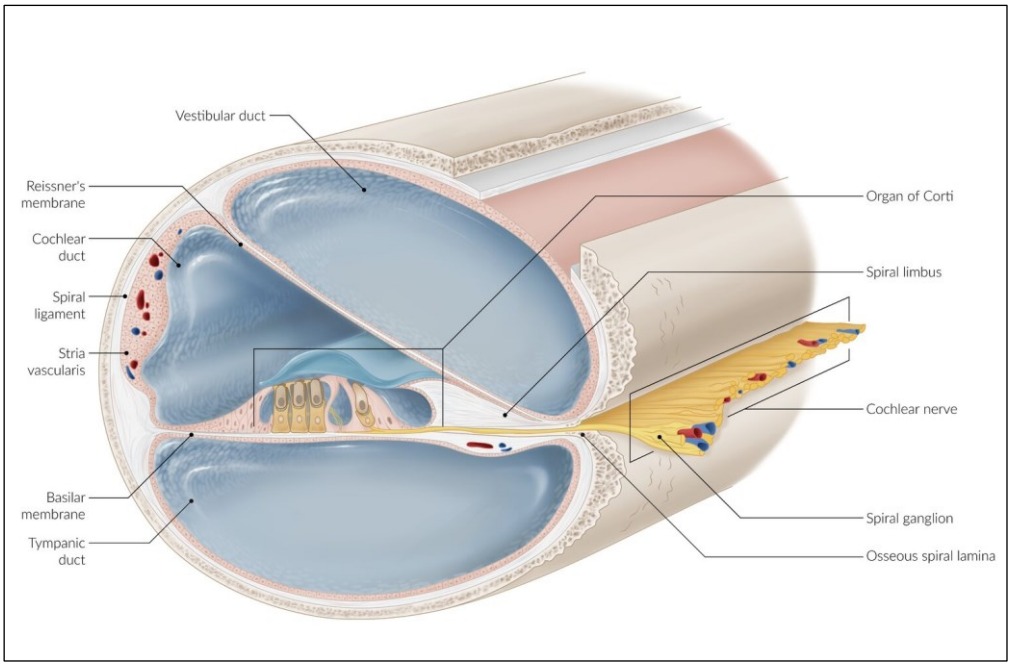

Figure 2- cross section of the cochlea (4)

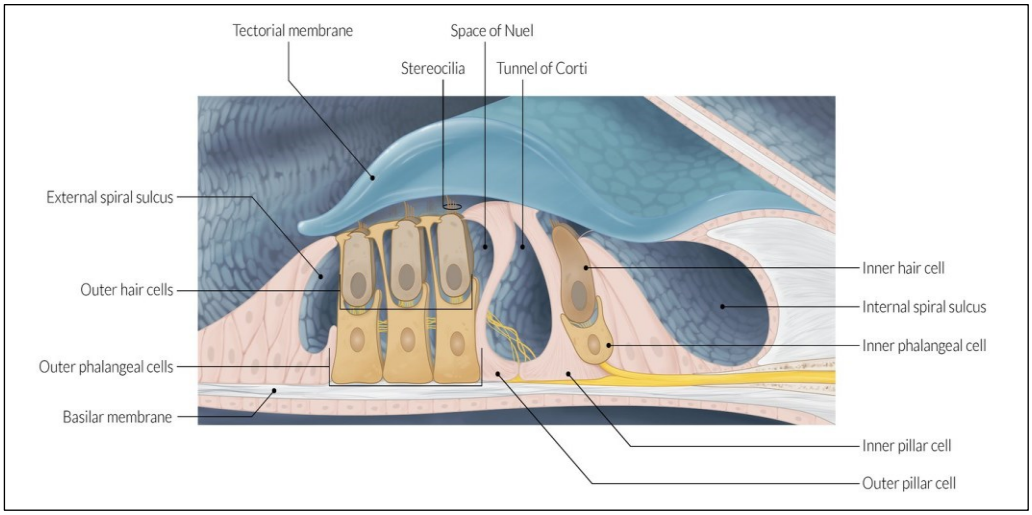

Figure 3- organ of corti (4)

5. What is congenital hearing loss

The range for normal hearing spans from 0 to 20 decibels (dB), enabling the perception of sounds even softer than a whisper. Mild hearing loss is characterized by a range of 20-39 dB, while moderate hearing loss falls within the 40-69 dB range, severe hearing loss is between 70-89 dB, and profound hearing loss is defined as exceeding 90 db. (5) Congenital hearing loss (CHL) encompasses conductive, sensorineural (SNHL), and mixed hearing loss.

CHL can be unilateral or, according to a recent study about the etiological evaluation of hearing loss in the pediatric population, unilateral hearing loss accounts for 29% of cases. In contrast, bilateral hearing loss accounts for 71%. (6) SNHL is caused by an injury to the cochlea or auditory nerve comprising the inner ear. This can be attributed to genetic predisposition, which

may be syndromic such as Usher and Pendred syndromes, or non-syndromic such as GJB2 gene mutations. Moreover, infections such as CMV and Rubella also lead to SNHL. Sound waves cannot propagate efficiently through the ear in conductive hearing loss for various reasons. Maldevelopment of the middle or external ear can impede the conduction of sound waves. This can happen due to Treacher-collins syndrome. Mixed hearing loss is characterized by the presence of both conductive and SNHL components. It is frequently observed in clinical conditions such as Branchio-oto-renal syndrome. (7)

6. Syndromic hearing loss

Usher syndrome

One of the most prevalent syndromic causes of hearing loss is Usher syndrome (USH). USH is a relatively rare autosomal recessive inherited disorder with an estimated prevalence of 4 to 7 in 100,000 individuals. (8) USH is the most common cause of hereditary deafness and blindness that present concomitantly. (9) If both parents carry the identical abnormal Usher gene, there is a 25% probability of their offspring inheriting the disorder. Moreover, there exists a 50% probability that their offspring will become asymptomatic carriers and a 25% likelihood that their progeny will remain unaffected by the condition and not inherit the abnormal gene. (10) 10 genes have been associated with this syndrome. Those genes are typically responsible for one of the three subtypes.

USH type	Locus	gene name	Protein name	Predicted function
USH1	USH1B	*MYO7A*	myosin VIIa	Actin-based motor protein
	USH1C	*USH1C*	harmonin	PDZ scaffold protein
	USH1D	*CDH23*	cadherin 23	Cell adhesion
	USH1E	n/a	n/a	Unknown
	USH1F	*PCDH15*	protocadherin 15	Cell adhesion
	USH1G	*USH1G*	SANS	Scaffold protein
	USH1H	n/a	n/a	Unknown
	USH1J	*CIB2*	CIB2	Ca^{2+} and integrin binding
	USH1K	n/a	n/a	Unknown
USH2	USH2A	*USH2A*	usherin	Cell adhesion
	USH2C	*GPR98*	VLGR1 (aka GPR98, MASS1)	G-protein coupled receptor
	USH2D	*DFNB31* (*Whrn* in mice)	whirlin	PDZ scaffold protein
USH3	USH3A	*CLRN1*	Clarin-1	Auxiliary subunit of ion channels?
n/a	n/a	*PDZD7*	PDZD7	PDZ scaffold protein

Table 2- Usher syndrome genes(11)

The major symptoms are hearing loss or deafness and retinitis pigmentosa. Usually, children with USH are born with moderate to profound hearing loss. Another feature is severe balance disorder due to abnormality of the vestibular hair cells, which is responsible for detecting both head movement and gravitational forces. (10) USH is clinically classified into three types. Patients with Usher syndrome type 1 (USH 1) are characterized by congenital severe to profound deafness, balance problems including trouble sitting up and walking, and the onset of retinitis pigmentosa during the first decade of life. Retinitis pigmentosa is a progressive disease that damages the retina's photoreceptor cells, ultimately leading to vision loss and potential blindness. (11) Type 2 (USH2) is typified by the preservation of normal vestibular function and the onset of congenital moderate to severe hearing loss and Retinitis pigmentosa in the second decade of life. (11) Type 3 (USH3) is marked by normal congenital hearing, with hearing loss typically commencing during childhood. Loss of night vision commonly occurs in adolescence, with severe vision loss manifesting by middle age. The balance function remains unaffected. (11)

Alport syndrome

Ocular abnormalities and SNHL characterize Alport syndrome, a hereditary renal disease. Pathogenic variants in the COL4A5 gene, associated with X-linked Alport syndrome, represent 80% of all cases. Abnormal variants in the COL4A3 and COL4A4 genes are associated with autosomal dominant (5%) and autosomal recessive (15%) modes of inheritance. (12) According to a study from 2018 about the mechanisms of the onset of Alport syndrome conducted by the Japanese Society of pediatric nephrology. X-linked Alport syndrome hematuria is observed in all male cases. In females, it's observed in ~98% with hematuria and 73% with hematuria and proteinuria. About 90% of patients develop end-stage renal disease by age 40. In females, approximately 12% of cases progress to end-stage renal disease by age 40. The onset of sensorineural hearing loss commonly arises during the latter stage of childhood (12). A substantial proportion of male patients, around 90%, exhibit hearing impairment by the age of 40 years. Conversely, the prevalence of this condition is lower among female patients, with only about 12% experiencing hearing loss by the same age. (12)

Autosomal recessive Alport syndrome (ARAS) does not exhibit gender differences in clinical manifestations and incidence. In families with monoallelic variant carriers, there is typically an absence of symptoms or only microscopic hematuria and mild proteinuria present. It is essential to analyze at least one familial member for a genetic diagnosis of ARAS. Ideally, both

parents confirm the presence of two heterozygous variants in trans positions on two different alleles (COL4A3 or COL4A4). Sensorineural deafness typically develops at a median onset age of 20 years. In autosomal dominant Alport syndrome, eye lesions and hearing loss were reported to occur rarely. About 10% of people with familial focal segmental glomerulosclerosis are found to have mutations in COL4A3 or COL4A4 genes, indicating that there may be numerous undiagnosed cases of autosomal dominant Alport syndrome (12). A combination of clinical features, including microscopic hematuria, proteinuria, and end-stage renal disease, characterizes the Alport syndrome. In addition, hearing impairment is observed, affecting roughly 55% of affected males and 45% of affected females. Notably, hearing loss in Alport syndrome is not present at birth and is typically diagnosed during early childhood or adolescence. Audiometry is an effective diagnostic tool for detecting hearing loss at an early stage, with a bilateral reduction in sensitivity to tones within the range of 2000-8000 Hz being a common finding (13).

Waardenburg syndrome

Waardenburg syndrome (WS) is an autosomal dominant genetic disorder that is caused by various mutations in different genes that, as a result, cause abnormal function of the neural crest. There are four types of WS with various mutations and clinical features. Mutations in PAX 3 gene on chromosome 2q is responsible for WS type 1. This type is characterized by dystopia canthorum, short philtrum, short retro-positional maxilla, and broad nasal root. WS Type 2 is subdivided into four subtypes. (14) Type 2A, 2B, and 2C are associated with mutations in the MITF gene on chromosomes 3q, 1q, and 8q.

In contrast, WS type 2D is associated with mutations in the SNAI2 gene on chromosome 8q. Generally, type 2 is characterized by sensorineural deafness, different colored irises, and specific location of canthi in contrast to WS type 1. WS type 3 as type 1 is caused due to mutations in PAX 3 gene on chromosome 2q. This type is characterized by the same features as type 1 and more pronounced musculoskeletal peculiarities such as aplasia of the 1st and 2nd ribs, sacral cysts, not fully differentiated small carpal bones, and hypoplasia of muscles with syndactyly. In certain instances, individuals may also present with microcephaly and cognitive impairment in addition to the mentioned features. WS type 4 is caused by mutations in EDNRB or endothelin three genes. This type has similar features as type 2. In addition, this type is associated with Hirschsprung disease (congenital megacolon).(14)

Pendred syndrome

Pendred syndrome (PS) is a hereditary disorder that follows an autosomal recessive inheritance pattern, and it is clinically distinguished by the occurrence of sensorineural hearing loss and thyroid goiter, with or without hypothyroidism. The genetic basis of the disease is attributed to a mutation in the SLC26A4 gene, which encodes the Pendrin protein. (15) PS is estimated to have a prevalence rate of 7.5 to 10 per 100,000 individuals constituting up to 10% of congenital deafness cases. (16) pendrin protein is important in inner ear function due to its expression in the vestibule and the cochlea. There is a crucial role in regulating endolymph resorption and acid-base balance. (15) The severity of hearing loss in Pendred syndrome patients typically ranges from mild to profound and can worsen progressively. Early indicators comprise a lack of response to sound or delay in language acquisition. (17) Molecular genetic testing is the definitive diagnostic test for PS. (16) The management plan is based on the individual's clinical features and may involve interventions such as providing hearing aids and CI. (18) Patients with PS require genetic counseling regarding potential offspring outcomes. Molecular genetic testing serves as the definitive diagnostic test for PS. At present, there is no known curative cure for PS. (18)

Treacher-Collins syndrome

Treacher-Collins syndrome (TCS) is an uncommon, autosomal dominant genetic disorder with a prevalence of 1 in every 50,000 live births .(19) Most frequently caused by mutations in the TCOF1 gene or the POLR1D gene. (20) TCS is characterized by craniofacial abnormalities and external ear deformities. These include microtia hypoplasia of the zygomatic arch, micrognathia (small lower jaw), retrognathia (posterior mandibular positioning), and cleft palate. Those abnormalities could lead to feeding and respiratory problems. External ear abnormalities include atresia of the external auditory canals and hypoplasia of the ossicles. As a result, individuals with TCS often experience bilateral conductive hearing loss. (19) The diagnosis of TCS involves a comprehensive evaluation that involves identifying the aforementioned clinical features and detecting pathogenic variants within the TCOF1 and POLR1D genes. (20) Genetic testing for TCS uses gene-targeted and comprehensive genomic testing. Serial single-gene testing involves sequence analysis of TCOF1 to detect intragenic deletions or duplications for TCOF1 and POLR1D. (20) Chromosomal microarray analysis can detect large deletions or duplications that sequence analysis cannot detect. A multigene panel that includes TCOF1, POLR1B, POLR1C, and POLR1D is used to identify the genetic cause

of the condition. Comprehensive genomic testing, such as exome sequencing and genome sequencing, may be considered when TCOF1 sequence analysis does not reveal a pathogenic variant. (20) Genes included in multigene panels and the gene sensitivity of the testing used for each gene can vary by laboratory and may change over time. In addition, some multigene panels may include genes not associated with TCS, and some laboratories may offer custom laboratory-designed panels or phenotype-focused exome analysis.

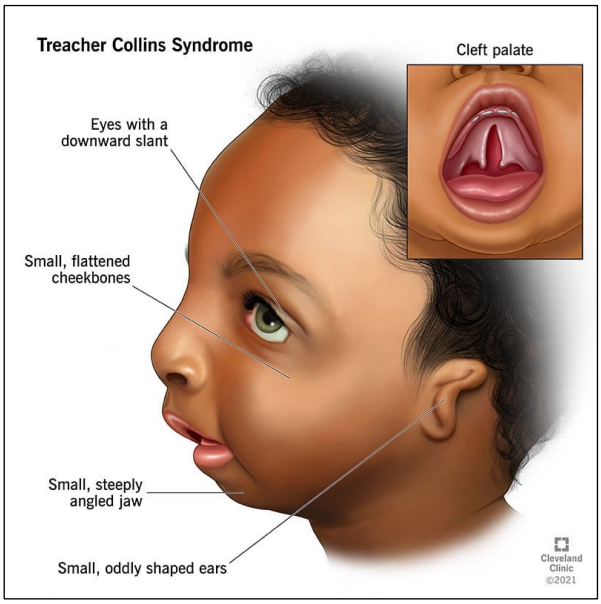

Figure 4- clinical features of TCS. (21)

Adapting treatment to the specific age group and severity of each patient's condition is crucial. The most critical concern is airway obstruction; endotracheal intubation is typically the preferred approach. Nevertheless, this procedure can sometimes be challenging or unfeasible because of the difficulty in visualizing the larynx and correctly placing the endotracheal tube. Therefore, tracheostomy is often necessary to secure the airway of any child with oropharyngeal obstruction. (22) This procedure can bypass the upper airway, allowing the child to breathe through their neck and alleviate the airway obstruction. Once the tracheostomy is in place, it can be challenging to remove or decannulate it until the child reaches the age of five. Complications associated with tracheostomy include airway scarring and stenosis, speech delays, difficulties with swallowing, recurring tracheitis, and even sudden death. (22) A comprehensive approach to hearing loss treatment may involve speech therapy, educational intervention, and bone conduction amplification. For individuals with ear anomalies, Bone Anchored Hearing Aids (BAHA) can serve as an alternative to bone conduction amplification. Cleft palate repair can be performed at the age of two; craniofacial reconstruction may be required between ages three to 12 years, including zygomatic and orbital reconstruction (20).

External ear reconstruction should precede reconstruction of the external auditory canal or middle ear and should be performed after the age of six years. The external auditory canal and middle ear reconstruction should be considered for individuals with bilateral microtia and narrow ear canals. Eyelid reconstruction using redundant upper eyelid skin can correct a downward-slanting fissure, and regular follow-up by an audiologist, ophthalmologist, and dentist is recommended. (20)

Branchio-oto-renal syndrome

Branchio-oto-renal syndrome (BORS) is an inherited autosomal dominant disorder caused by mutations in the EYA1, SIX1, or SIX5 genes, leading to structural defects in the outer, middle, or inner ear. Usually result in sensorineural, conductive, or mixed hearing loss, with mixed hearing loss being the most prevalent form among BORS patients, accounting for 52% of all hearing loss cases. (23) Other clinical manifestations may include branchial fistula and cysts, preauricular pits, and renal malformations that can progress to end-stage renal disease later in life. Diagnosis of BORS is based on clinical findings and genetic testing, including gene-targeted and comprehensive genomic testing. EYA1 mutations are detected in approximately 40% of individuals with BORS. (23) Treatment for BORS is tailored to each patient's specific symptoms and features. It may include hearing aids or CI, surgical removal of branchial cleft cysts or fistulae, and managing kidney abnormalities such as renal failure. Speech and language therapy and regular monitoring and screening for associated conditions may also benefit affected individuals. (24)

7. non-syndromic hearing loss

Mutations in the GJB2 gene at the DFNB1 locus on chromosome 13q12 are the most common cause of non-syndromic hearing loss. This gene encodes for connexin-26 (Cx26), a gap junction protein crucial for intercellular communication among supporting cells in the cochlea. Cx26 serves this vital function and is essential in regulating the balance of cochlear fluids, including endolymph and perilymph, necessary for maintaining proper auditory system function. (25) GJB2 gene mutations account for 50% of autosomal recessive non-syndromic hearing loss. (26) More than 100 mutation variants are associated with the GJB2 gene, but there is some predominance in given populations. 35delG, more common in individuals of northern European descent in the 167delT, is the most common variant in the Ashkenazi Jewish population, and 235delC is the most common variant in the Japanese population. (23) The diagnosis of DFNB1 can be confirmed in an individual exhibiting mild-to-profound CSNHL

impairment, which is typically non-progressive. This diagnosis is made with biallelic pathogenic variants within the GJB2 gene. Molecular genetic testing can employ various techniques, including gene-targeted testing, single-gene testing or multigene panels, and comprehensive genomic sequencing. (27) The recommended interventions for managing severe-to-profound congenital deafness include obtaining suitable hearing aids, enrolling in an appropriate educational program for the hearing impaired, and considering CI as a potential option for habilitation.

8. Infectious etiology

Cytomegalovirus

Several congenital infectious agents are associated with acquired hearing loss. Cytomegalovirus (CMV) is a major non-genetic contributor to congenital infections worldwide, with the prevalence being higher in countries with high rates of maternal seroprevalence. The main transmission routes are sexual contact and exposure to body fluids such as blood, urine, semen, or vaginal secretions. An infected mother can potentially infect the fetus by transplacental transmission. The likelihood of a congenital CMV infection is at its highest when there is a primary infection during pregnancy, which can result in a vertical transmission risk of 32%. (28) In the USA, congenital CMV infection incidence is 1 in every 200 births. (29) Most infants infected with CMV do not present any symptomatic abnormalities during the neonatal period. However, about 10% of infants with congenital CMV have symptoms present at birth. Some symptoms include microcephaly, rash, jaundice, low birth weight, hepatosplenomegaly, seizures, and retinitis. (29) Some signs are associated with hearing loss, specifically in babies, such as a baby that doesn't react to a source of sound after six months of age, can't say any single word like "mama" or "dada" by one year of age or don't turn their head in reaction to sound, when the baby appears to hear some sounds but not others. Children with symptomatic CMV infections may exhibit additional symptoms, such as speech delays, unclear speech, difficulty following directions, and a propensity to turn up the volume on the television or music. (29) Infants who develop symptomatic CMV infections are at a higher risk of developing neurodevelopmental sequelae and SNHL. (30) There are a few pathophysiological mechanisms that are suggested for the underlying cause of sensorineural hearing loss resulting from CMV infections which include immune responses by increasing ROS and activating NLRP3 inflammatory cells and virus-induced labyrinthitis that damage the vestibular endolymphatic system and organs leading to a collapse of the saccular membrane

Rubella

Rubella is a single-stranded RNA virus from the Togoviridae family, commonly known as German measles. Transmitted via contaminated upper respiratory tract through respiratory droplets generated during coughing, sneezing, and close contact communication. (31) Pregnancy-associated infection, primarily during the first trimester, may impact multiple organs, resulting in congenital rubella syndrome and associated birth defects. CRS is primarily characterized by various congenital anomalies, including sensorineural hearing impairment, eye disorders such as cataracts, congenital glaucoma, or pigmentary retinopathy, as well as cardiac malformations such as patent ductus arteriosus or peripheral pulmonic stenosis, which are the most observed anomalies. (32) The most frequent consequence of CRS is congenital sensorineural hearing loss, which is observed in around 60% of affected cases, mainly when infection transpires during the fourth gestational month.. (32) Before the advent of vaccination, rubella was a prevalent disease with periodic outbreaks every 6 to 9 years. Without immune protection, pregnant women were at risk of contracting rubella, which would lead to the development of CRS cases in their offspring. Following the introduction of live attenuated rubella vaccines in 1969, the US implemented a comprehensive vaccination program to prevent congenital rubella infections. (33) In 2004, after a thorough review of rubella epidemiology, an expert panel declared that rubella elimination had been achieved in the US. (34) Consequently, from 2005 to 2017, the number of reported CRS cases in the US substantially decreased to less than one per year. (33)

9. Screening and evaluation

The ability to perceive, develop, and utilize verbal language is closely linked to auditory function. Even mild hearing loss can impede speech and language development in children with hearing impairments, delaying the acquisition of linguistic, social, academic, and sensory skills. (35) Unlike normal-hearing children, who acquire language naturally through daily interactions, hearing-impaired children require specialized training tailored to the degree of their hearing loss to achieve typical language acquisition and prevent language disorders. (36) In the previous century, neonatal hearing screening was limited to targeted screening only of infants at high risk for hearing loss. However, with mounting evidence indicating the positive effects of early detection of hearing loss on child development, there has been a shift toward universal neonatal hearing screening programs. (7) Screening programs offer several advantages, including detecting congenital hearing loss earlier than caregivers and clinicians,

who may only notice delayed speech and language development at a later stage. (36) Early identification and intervention of permanent hearing loss in infants have enhanced language and developmental outcomes. This is because early diagnosis facilitates the timely introduction of hearing aids. (37) A study conducted in England on a large birth cohort of 120 children with bilateral permanent hearing loss revealed that children whose hearing loss was confirmed before the age of nine months exhibited better receptive and general language abilities as compared to those diagnosed after the age of nine months. (38) The follow-up reports further demonstrated that patients diagnosed before nine months had superior reading and communication skills compared to those diagnosed after nine months throughout their adolescent years. (38)

The evaluation of auditory function through audiometric assessment is essential in diagnosing hearing loss, determining its extent and sidedness, and whether it affects one ear or both. Audiometric assessment involves the use of electrophysiological and behavioral tests. The electrophysiological tests include OAE, which examines the function of outer hair cells, and AABR, which evaluates inner hair cells' function and the auditory pathways' integrity. (7) The behavioral tests include audiometry, which measures the perception of sounds by the patient. The screening can be performed by measuring OAEs twice, measuring OAEs and AABRs, or measuring AABRs twice. Infants who do not pass hearing screenings should receive prompt audiological and medical evaluation before three months of age. (7) Oto-acoustic emissions are sounds caused by the motion of the outer hair cells as they energetically respond to auditory stimulation. The oscillatory sound pressure waveform seen in a transient evoked OAE response corresponds to the motion of the tympanic membrane being pushed back and forwards by fluid pressure fluctuations generated in the cochlea as their detection requires adequate sound transmission to and from the cochlea. (7) Spontaneous Oto-acoustic emissions (SOAE) are physiological and acoustic emissions produced by the outer hair cells of the ear, which propagate through the auditory ossicles and tympanic membrane to reach the auditory canal. On the other hand, Evoked Oto-acoustic emissions (EOAE) are acoustic emissions that arise in response to acoustic stimuli. In terms of interpretation, detectable OAE indicates normal outer hair cell function and intact cochlear function. Conversely, the absence of OAE suggests cochlear hearing loss greater than 30 dB. (39)

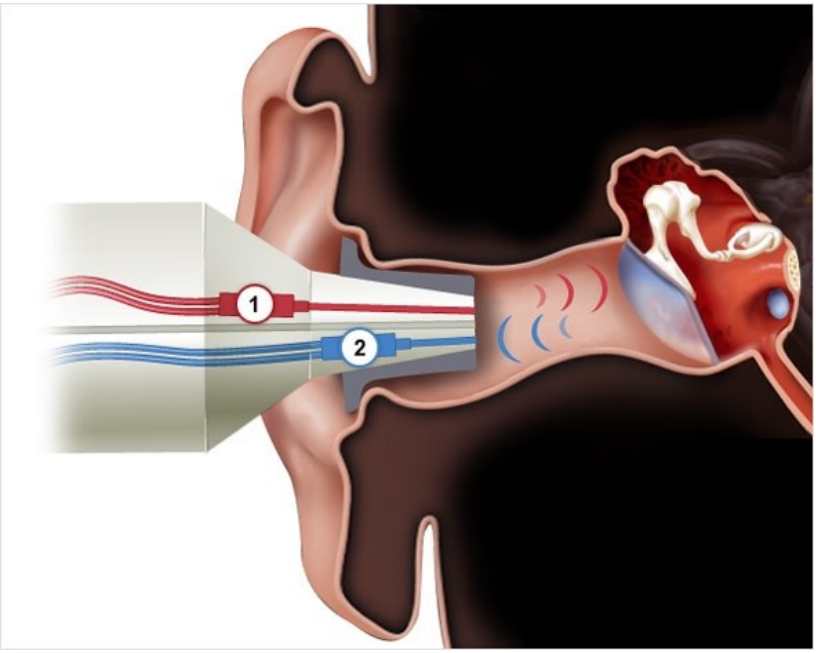

Figure 5- Otoacoustic emission (40)

Auditory brainstem response (ABR) is a type of evoked potential that can identify hearing impairment in the cochlea, auditory nerve, and brainstem. AABR measurements involve placing surface electrodes on the forehead and recording neural activity in response to sound stimuli. The results are compared to a standard AABR template and classified as "pass" or "fail." AABR is helpful in distinguishing between conductive and sensorineural hearing loss. (41)

Figure 6- Auditory brainstem response (42)

Visual reinforcement audiometry (VRA) is a commonly used technique for testing hearing in infants aged 6-24 months. In VRA, the infant is conditioned to respond to a sound stimulus by turning their head towards the sound source, which is accompanied by a reinforcing visual stimulus.

Play audiometry is another technique often used in children aged 2-4. It involves conditioning the child to respond to auditory stimulation through play activities, such as placing a toy in a box when they hear a sound. In individuals beyond the age of four years, conventional audiometry methods are commonly used, by either an air-conduction transducer (such as an earphone) or a bone-conduction transducer, or both, to assess hearing. (7) A thorough audiological and etiological evaluation is necessary When a newborn does not pass the hearing screening, and congenital hearing loss is suspected. Detecting the potential origins of such impairment can be achieved through genetic and perinatal examinations and assessments for congenital infections. Of these infections, congenital cytomegalovirus (CMV) warrants particular attention, as it is the primary infectious agent responsible for hearing loss. (7)

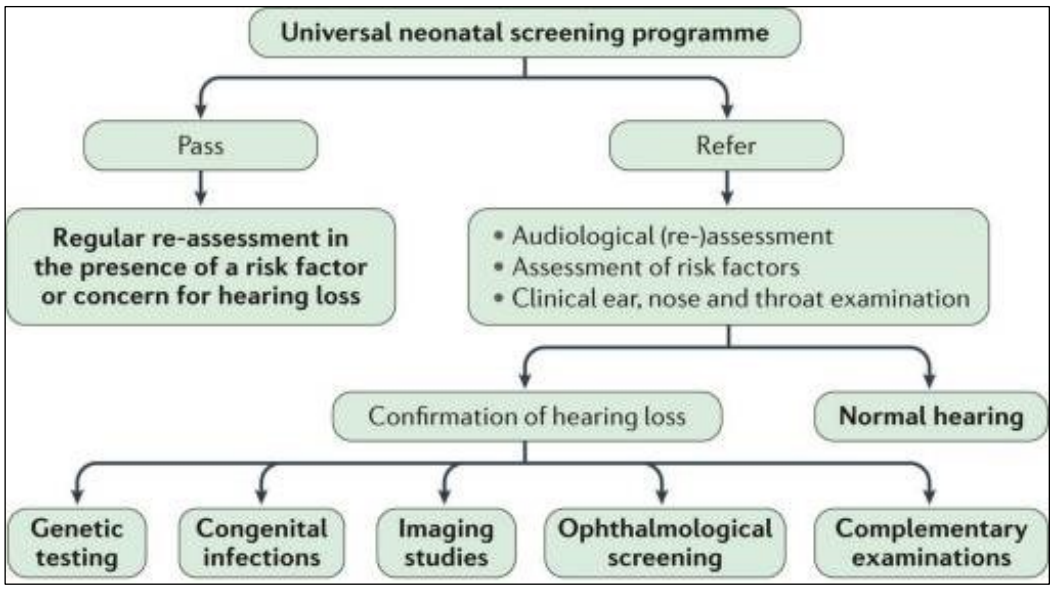

Figure 7- A multidisciplinary algorithm for evaluation of hearing function in infants (7)

10. Treatment

Although no cure exists for hearing loss, several approaches exist, such as hearing aids for mild cases and CI for profound to severe cases. Utilizing these interventions may result in a hearing sensation sufficient to enable patients to develop nearly normal speech patterns. However, such interventions may not fully replicate the experience of natural hearing.

A hearing aid is an electronically driven apparatus that amplifies and transmits acoustic signals along the auditory pathway to target the inner and outer hair cells on the cochlea's basilar membrane. The device typically comprises a microphone, amplifier, and speaker. To function, it captures sound from the surroundings, amplifies it following the user's settings, and then

delivers it into the outer ear via a suitable mechanism. (43) There are two primary options for delivering sound through hearing aids. Air-conduction hearing aids are the traditional type that transmits sound through the air-conduction auditory pathway, encompassing the outer, middle, and inner ear structures. (43) Conversely, bone conduction hearing aids are the preferred alternative for individuals with outer and middle ear impairments. These devices direct sound through the bone conduction pathway, which passes through the temporal bone and directly into the inner ear without involving the outer and middle ear structures. Typically, bone conduction hearing aids are worn on a hard or soft headband. (43) There are various hearing aid types, and selecting the optimal hearing aid should be personalized. To provide maximum benefit, the physician must consider individualized factors, including the audiometric deficit, such as laterality, frequency, degree of hearing loss, cosmetic preferences, and the patient's lifestyle. The most popular choice is a behind-the-ear (BTE) hearing aid behind the pinna capable of various amplification modes and easily adaptable to the patient's needs, providing many advantages, including affordability and ease of use. Other types include custom-shaped types such as in the ear (ITE), in the canal (ITC), and entirely in the canal (CIC). These are the most discrete and preferred by patients who wish for an improved aesthetic and can be used for a range of hearing deficiencies by improving the amplification of high frequencies due to the closer proximity of the receiver to the eardrum. However, it may not be an appropriate option for everyone, as higher amplification levels can quickly drain the battery. (44) This is useful for speech discrimination in crowded environments with high background noise levels. (45) A receiver in the canal (RIC) is another type of hearing aid that is similar to BTE, except the receiver sits in the canal, thus allowing higher amplification levels without risk of acoustic feedback, meaning that the sound does not escape the canal, making RIC more suitable for patients with high-frequency deficiency also known as 'ski-slope' hearing referring to the curvature shown on an audiogram which is seen in presbycusis which is the most common type of HL associated with age. A significant downside of RIC is the susceptibility to distortion by ambient sound, patients who experience frequent ear infections and is prone to bio-degradation due to it being exposed to cerumen. (44)

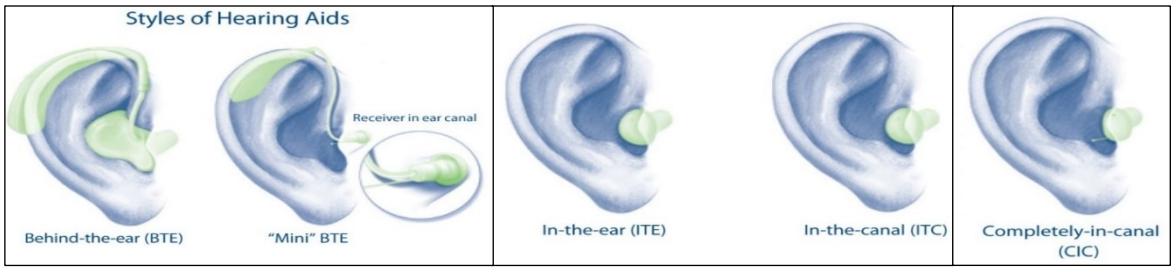

Figure 8 – Styles of hearing aids (46)

There are two main types of bone-conducting hearing aids: surgical and non-surgical. They convert acoustic sound waves into mechanical vibrations via direct contact with the skull that carries the vibrations to the inner ear. Surgical hearing aids are chosen according to the indications, including percutaneous and transcutaneous options. Percutaneous has advantages, including signal attenuation up to 20 dB, especially at high frequencies but poses a potential risk of adverse skin reactions.

Transcutaneous devices are designed to avoid cosmetic concerns and skin complications by implanting the titanium device beneath the skin. An external device attached by a magnet is then activated, vibrates in response to sound impulses, and carries the soundwave to the implanted portion. (47) The magnetic force required to hold the external device in place can lead to pain and irritation of the intervening skin and soft tissue, as stated in a 2016 systematic review by Mohamed et al. that shows a skin complication rate ranging from 9.4 to 84%. (48) Non-surgical devices, also known as 'extrinsic,' attach to the patient via a headband, adhesive, eyeglasses, or another mechanism and is in direct contact with the skin and transmit vibrations in response to sound to intact skin and soft tissue to the skull leading to bone conduction hearing. A prominent advantage of this device is that it is a non-surgical option and can be used to evaluate the pre-implantation testing before bone-anchored hearing aids, while a disadvantage of this device is that depending on the force required to hold the device, it may limit wear time. (47)

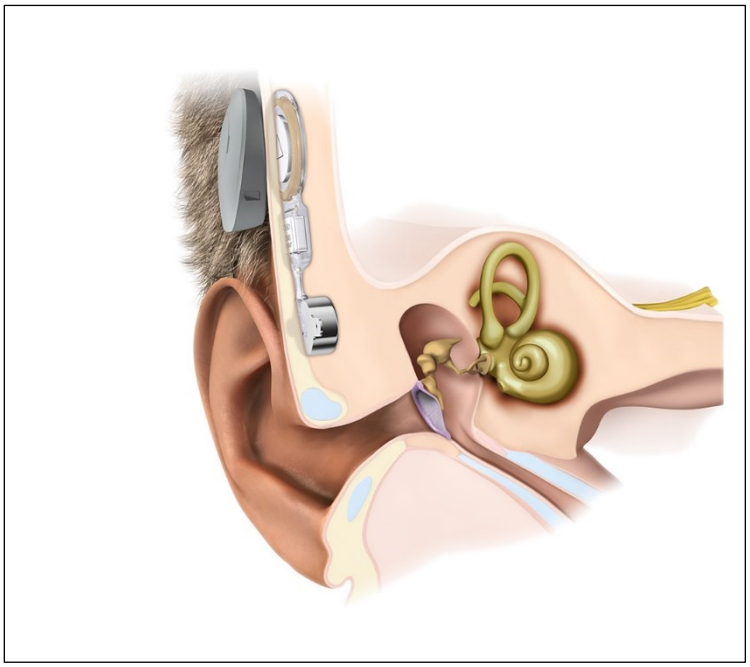

Figure 9- Bone anchored hearing aid (49)

Figure 10- non-surgical bone conduction device (50)

CI are implanted devices that stimulate the spiral ganglion cells of the auditory nerve by electrical pulses by converting external sound waves to electrical signals to the hearing nerve, thereby evading the damaged hearing mechanism. It is considered a new technology rapidly evolving in medicine and poses a challenge to optimal patient selection. Still, it is considered the most successful implantation device for sensory deprivation. (51) Indications for choosing a successful candidate are medically determined by the FDA, including patients greater than six months of age, SNHL, cochlear and cranial nerve VIII with relatively preserved anatomy, and more. (52) Contraindications to CI are patients who cannot tolerate general anesthesia and patients who may be better served by hearing aids, such as those with conductive hearing loss. The procedure is done following CT or MRI to explore the anatomy. Then the side of implantation is selected by choosing the better surgical ear. However, studies suggest that regardless of audiometric differences, it may not matter which ear receives the implant. (53) During the implantation surgery, a mastoidectomy is performed to visualize the round windows of the cochlea. A processor is placed under the temporal fascia, and the electrode is inserted into the appropriate position through the round window and aligned with the cochlea, which is tested by an audiologist. Finally, an X-ray is taken to confirm placement, and the skin is sutured. (51)

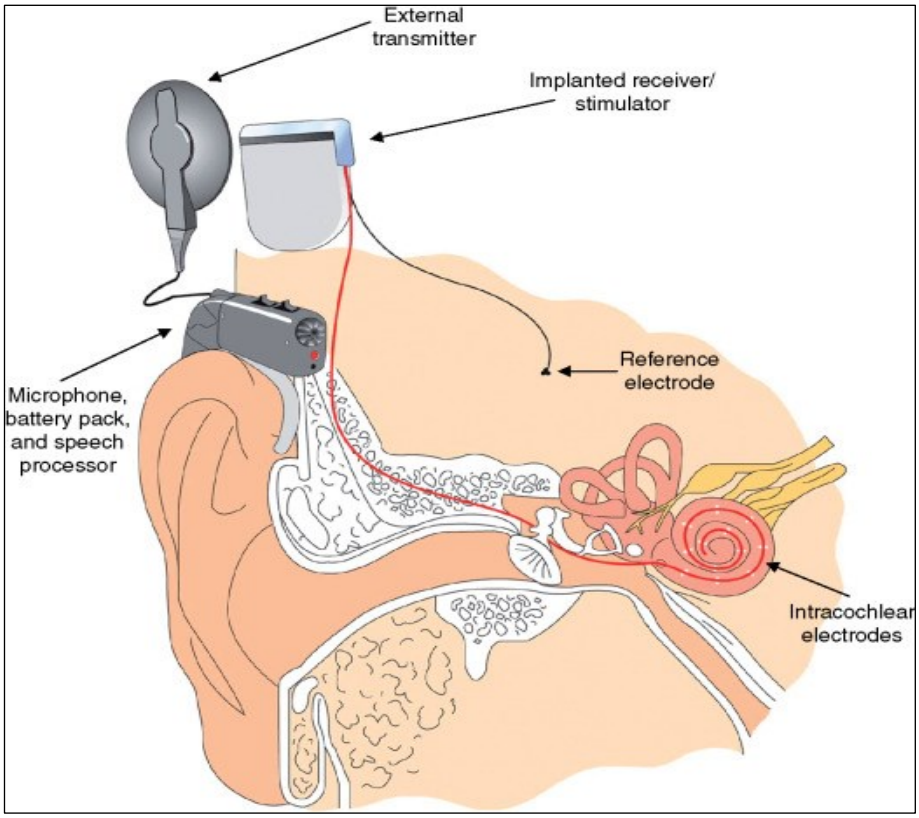

Figure 11- cochlear implant (54)

CI may be challenging in patients with internal ear anomalies. According to Onan et al.(55) a study of 55 patients with inner ear malformation was conducted to evaluate the intraoperative and postoperative findings and auditory performance. In 30 out of 55 patients, Hearing capabilities were tested. The evaluation involved three groups of patients. The first group comprised individuals with cochlear abnormalities, the second group consisted of individuals with vestibular malformations, and the third group included individuals with a normal bone labyrinth. The study found that group I performed significantly less on the listening progress profiles test and the meaningful auditory integration scale test than the other groups. Specifically, group I had lower scores on the listening progress profiles test in the 12th and 18th month ($P < .05$), although performance improved and reached similar levels to the other groups after 24 months. The meaningful auditory integration scale test also showed significantly lower performance for group I in the 24th and 36th month ($P < .05$). Furthermore, the study observed that perilymph gusher, which is the flow of perilymph and cerebrospinal fluid after the surgical opening of the labyrinth, was associated with incomplete partition I malformation in three patients.

In contrast, oozing was observed in 50% of incomplete partition II patients. In conclusion, patients with inner ear anomalies initially exhibited a worse level of language development than patients with normal bone anatomy but eventually reached the same level over time.

Nonetheless, patients with inner ear malformations are at a higher risk for facial nerve anomalies and postoperative meningitis.

11. Outcome

Early implantation before 12 months of age may improve speech perception. This is shown clearly in Dettman et al. (56) who analyzed speech perception, language skills, and speech production among children implanted between 6 and 12 months (n = 151), 13 and 18 months (n = 61), 19 and 24 months (n = 66), 24 and 42 months (n = 82), and 43 and 60 months (n = 43) and concluded a significant relationship between the age of implantation and speech perception by evaluating Clinical Evaluation of Language Fundamentals (CELF) and Preschool Language Scale (PLS) protocols which resulted in a more significant percentage of children demonstrating superior language performance within the normative range by school entry. This, in conjunction with speech therapy, has shown to be optimal for further improved outcomes and higher language scores. (57)

Although modern hearing devices are highly sophisticated, they cannot fully replicate the functionality of a typical auditory system. Consequently, complementary therapeutic care remains necessary. There are two main language skill techniques with the evolving approach towards language and communication support. Oral spoken language is preferred because more than 90% of deaf children have parents with intact hearing. (58) The second option is sign language, which is logically preferred by deaf parents or when children cannot develop oral language skills even after using a hearing aid. Various techniques enhance the child's ability to communicate effectively across diverse social contexts, promoting their overall well-being and quality of life. Some of them include auditory training is a method that helps to improve skills of discrimination, recognition, comprehension, and working memory. As a result, the child will better perceive, analyze, and comprehend sound stimuli, including environmental and speech sounds. (59) Another communication technique utilized in speech therapy is cued speech, which involves using hand gestures to supplement speech sounds. Hand shapes are used to represent consonants, while the placement of the hands around the face means vowels. The ease of learning and mastering cued speech within three months makes it a convenient option for many patients seeking alternative communication techniques. (58)

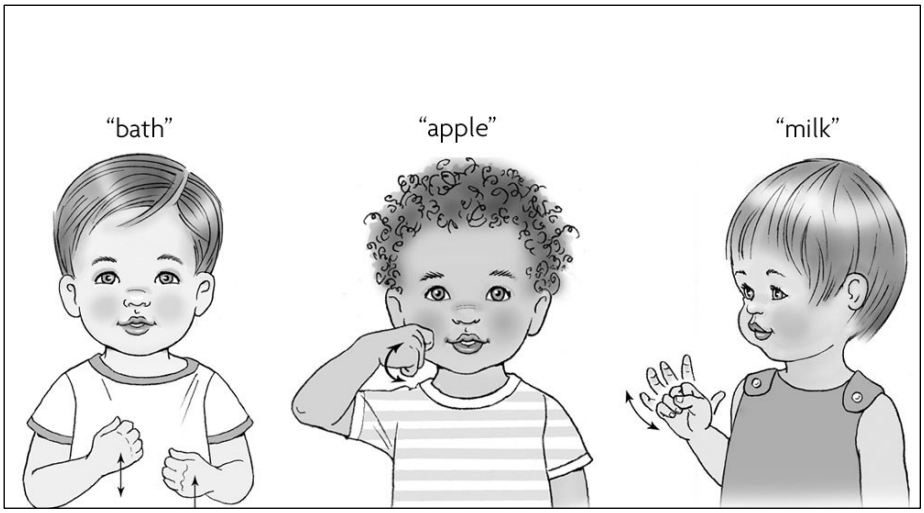

Figure 12- cued speech (60)

The Sign Language approach promotes visual communication, using sign language for effective communication. This method recognizes that for individuals who are deaf, visual communication is often their primary and most natural mode of communication and thus can be a valuable tool for facilitating language development. Sign language has different grammar, vocabulary, and expressions. It is grounded in the principle that visual communication can provide a means for individuals who are deaf to participate fully in society. (58)

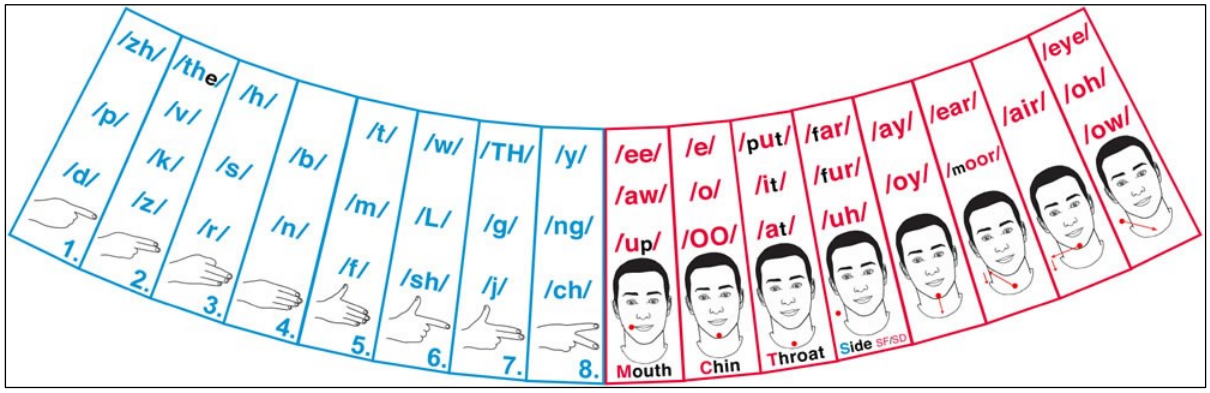

Figure 13- sign language in babies (61)

The Joint Committee on Infant Hearing suggests that clinicians should adopt a flexible approach by offering various communication options tailored to the individual needs of the patient instead of a standardized rehabilitation approach. Finally, it is imperative to consider the child's perspective as they grow older to ensure their rights are respected. (62)

12. Conclusion

The findings of this study underscore the crucial role of early screening and intervention in managing congenital hearing loss, with a significant impact on long-term outcomes for affected individuals. Implementing screening programs offers several advantages, enabling the detection of hearing loss at an earlier stage than caregivers and clinicians who may only recognize delayed speech and language development later. Moreover, research has shown that early cochlear implantation, mainly before 12 months of age, can significantly enhance speech perception. There is a positive association between the age of implantation and speech perception, indicating that earlier implantation results in superior language performance within the normative range when children enter school. Together with speech therapy, this approach has proven optimal for achieving improved outcomes and higher language scores. Ongoing research and technological advancements are essential to enhance further treatment options and outcomes for individuals with congenital hearing loss. Investing in innovative approaches, such as improved cochlear implant technology and speech therapy techniques, can lead to better long-term results. Implementing new advancements in screening and therapy can further enhance the overall outcome for affected individuals with congenital hearing loss.

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