Etiopathogeny of congenital and early-onset hearing loss; detection and early intervention methods in infants and children

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\textbf{ABSTRACT}

Screening is one of the most important methods of early diagnosis of treatable diseases in children. Hearing loss is one of the most common congenital anomalies, occurring in approximately 1-3 infants per 1000 (1). The prevalence of hearing loss has been shown to be greater than that of most other diseases and syndromes (eg, phenylketonuria, hypothyroidism) screened at birth.

Hearing loss, especially mild and moderate forms, may not be recognized before the second year of life, but may produce great defects in conversational abilities. Early identification and intervention can prevent severe psychosocial, educational, and linguistic repercussions. Infants who are not identified before 6 months of age have delays in speech and language development. Intervention at or before 6 months of age allows a child with impaired hearing to develop normal speech and language, like his or her hearing peers.

\textbf{Key words:} congenital hearing loss, screening, early intervention

\textbf{INTRODUCTION}

The main goal of early hearing detection and intervention (EHDI) is to maximize linguistic competence and literacy development for children who are deaf or hard of hearing. Without appropriate opportunities to learn language, these children will fall behind their hearing peers in communication, cognition, reading, and social-emotional development (2).

To avoid these developmental delays, which may result in poorer educational and employment achievement in adulthood, the guidelines (The Joint Committee on Infant Hearing-JCIH) recommend screening of hearing of all infants at no later than 1 month of age.

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For those who fail screening, a comprehensive audiologic evaluation should take place no later than 3 months of age, and those with confirmed hearing loss should receive appropriate intervention no later than 6 months of age. Treatment should be guided and administered by healthcare and education professionals with expertise in hearing loss and deafness in infants and young children (3). Hearing loss has no physical characteristics and the child with hearing loss looks normal and often achieve normal early milestones, including babbling. So, we can call the hearing loss an invisible handicap diagnosed by parents around 24 months of age.

Before we can understand hearing loss, we must first understand what hearing entails. Hearing is one of the five senses, and refers to the ability to detect the vibrations of particles against the ear drum. There is evidence that the human fetus responds to sounds as early as 22 weeks gestational. Although the development of the cochlea and inner ear active mechanisms is complete at birth, the central auditory pathway need further maturation, a process which is retleted to and dependent upon auditory stimulation (4). When we hear sounds, we really are interpreting patterns of movement of air molecules. We can describe sounds in terms of their frequency (or pitch) and intensity (or loudness). Frequency is measured in hertz (Hz). A person who has hearing within the normal range, can hear sounds that have frequencies between 20 and 20,000 Hz. The most important sounds we hear every day are in the 250 to 6,000 Hz range. Speech includes a mix of low and high frequency sounds. Sounds that are louder than 90 dB can be uncomfortable to hear (5).

1. PRENATAL CAUSES / RISK FACTORS FOR HEARING LOSS

A. Genetic causes

1. Non-Syndromic Deafness

Non-syndromic means that deafness occurs in isolation, without other associated disorders. About 80% of genetic hearing loss is non-syndromic. In the past few years several loci have been mapped and 11 genes have been identified. Autosomal dominant loci are called DFNA, autosomal recessive as DFNB, and X-linked as DFN.

The 80–85% of genetic deafness are recessive. The parents are normal, not deaf, but carriers. On one chromosome, they have a normal gene and on the other chromosome, a mutated gene. They have the following probabilities: 25% chance to have deaf children, because these children present double copy of the mutated gene (each copy comes from one parent); 50% chance to have normal hearing children who are carriers (like the parents); 25% chance to have normal hearing children who are not carriers. It’s easy to understand why the consanguinity increase the risk of having a deaf child (6).

Non-syndromic deafness is highly heterogeneous, but mutations in the connexin-26 molecule (gap junction protein, gene GJB2) account for about 49% of patients with non-syndromic deafness and about 37% of sporadic cases (7).

2. Syndromic Deafness

Syndromic deafness, which accounts for the remaining 20% of congenital deafness, comprises an immensely complicated interlinked set of disorders. The descriptions here are only to give the general flavor of the diseases and are not meant to include all features of the disorders. Most frequent syndromes associated to hearing loss are:

- Alport syndrome’s classic phenotype is renal failure and progressive sensorineural deafness.
- Branchio-oto-renal syndrome is caused by mutations. This syndrome is characterized by hearing disturbances and cataract, branchial cleft fistulae, and preauricular pits.
- X-linked Charcot Marie Tooth is caused by a mutation in the connexin 32 gene. Usually clinical signs consist of a peripheral neuropathy combined with foot problems and “champagne bottle” calves. Sensorineural deafness occurs in some.

As noted above, the connexin gene is also associated with a large percentage of cases of non-syndromic deafness. There are several other associated neuropathies and deafness syndromes. Autosomal recessive demyelinating neuropathy, autosomal dominant hereditary neuropathies type I and II, and X-linked hereditary axonal neuropathies with mental retardation are all associated with deafness.

Oculoauriculovertebral dysplasia (OAVD) or Goldenhar’s syndrome includes a complex of features including hemifacial microtia, otomandibular dysostosis, epibulbar lipodermoids,
coloboma, and vertebral anomalies that stem from developmental vascular and genetic field aberrations.

*Jervell and Lange-Nielsen syndrome* is associated with cardiac arrhythmias. There is, by prolongation of the QT interval, torsade de Pointe arrhythmias, sudden syncopal episodes, and severe to profound sensorineural hearing loss.

*Mohr-Tranebjaerg syndrome* is an X-linked recessive syndromic hearing loss characterized by postlingual sensorineural deafness in childhood, followed by progressive dystonia, spasticity, dysphagia and optic atrophy. The syndrome is caused by a mutation thought to result in mitochondrial dysfunction. It resembles a spinocerebellar degeneration called Fredreich's ataxia which also may exhibit sensorineural hearing loss, ataxia and optic atrophy.

*Norrie disease* include specific ocular symptoms, progressive sensorineural hearing loss, and mental disturbance.

*Pendred syndrome* is deafness associated with thyroid disease (goiter).

*Stickler syndrome* is characterized by hearing impairment, midface hypoplasia, progressive myopia in the first year of life, and arthropathy.

*Treacher Collins syndrome* is characterized by coloboma of the lower eyelid, micrognathia, microtia, hypoplasia of the zygomatic arches, macrostomia, and inferior displacement of the lateral canthi with respect to the medial canthi.

*Waardenburg syndrome* type I and II include lateral displacement of the inner canthus of each eye, pigmentary abnormalities of hair, iris, and skin (often white forelock and heterochromia iridis), and sensorineural deafness.

*Usher syndrome* is characterized by hearing impairment and retinitis pigmentosa.

**B. Risk factors connected to pregnancy**

- intrauterin infections, especially TORCH (toxoplasma, rubella, cytomegalovirus, herpes) during pregnancy
- ototoxic medication (aminoglycosides, loop diuretics, quinine derivatives, etc.)
- alcohol and/or drug intake during pregnancy

**II. PERINATAL AND POSTNATAL CAUSES/ RISK FACTORS FOR HEARING LOSS (8)**

- prematurity (gestational age under 34 weeks, birth weight under 1500 g)
- severe perinatal hypoxia
- infections (in specially Pneumococcus, Haemophilus influenzae meningitis, encephalitis)
- hyperbilirubinemia (blood bilirubin level >20mg/dl)
- ototoxic drugs (aminoglycosides and furosemide administration more than 5 days without serum level monitoring)
- neonatal pulmonary hypertension – mechanical ventilation for 5 days or longer
- extracorporeal membrane oxigenation (ECMO)
- traumatism during delivery
- severe intracranian hemorrhage
- neonatal convulsion
- noise induced hearing loss (at preterms)

**III. TYPES OF HEARING LOSS**

Hearing loss can be categorized by where or what part of the auditory system is damaged (10).

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| 1. | Caregiver concern regarding hearing, speech, language or developmental delay |
| 2. | Family history of permanent childhood hearing loss |
| 3. | Neonatal intensive care more than 5 days or any of the following regardless of length of stay: ECMO, assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia that requires exchange transfusion |
| 4. | In utero infections, such as cytomegalovirus, herpes, rubella, syphilis and toxoplasmosis |
| 5. | Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits and temporal bone anomalies |
| 6. | Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss |
| 7. | Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteoporosis and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, Jervell and Lange-Nielson |
| 8. | Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome |
| 9. | Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis |
| 10. | Head trauma, especially basal skull/temporal bone fracture that requires hospitalization |
| 11. | Chemotherapy |

**TABLE 1.** Risk indicators associated with permanent congenital, delayed-onset, or progressive hearing loss in childhood according to the Joint Committee on Infant Hearing Year 2007 Position Statement (9)
A. Conductive Hearing Loss

Conductive hearing loss occurs when sound is not conducted efficiently through the outer ear canal to the eardrum and the tiny bones, or ossicles of the middle ear. Conductive hearing loss usually involves a reduction in sound level, or the ability to hear faint sounds. Conditions such as impacted cerumen or foreign bodies in the external ear canal, an atretic or stenotic ear canal, interruption or fixation of the ossicular chain, perforation of the tympanic membrane, otitis media with effusion, otosclerosis and cholesteatoma can cause conductive hearing loss (11).

B. Sensorineural Hearing Loss

Sensorineural hearing loss occurs when there is damage at the level of the inner ear (cochlea) or at the nerve pathways from the inner ear (retrocochlear) to the brain. In most cases the inner hair are affected in the organ of Corti. Congenital sensorineural hearing loss can be caused by intrauterin infections, birth injury, drugs that are toxic to the auditory system, and genetic syndromes.

Later onset sensorineural hearing loss can be caused by bacterial meningitis, ototoxicity (drug induced), intense or excessive noise, physical damage to head or ear.

Sensorineural hearing loss not only involves a reduction in sound level, or ability to hear faint sounds, but also affects speech understanding, or ability to hear clearly (12).

C. Mixed Hearing Loss

Conductive hearing loss occurs in combination with a sensorineural hearing loss. In other words, there may be damage in the outer or middle ear and in the inner ear (cochlea) or auditory nerve. When this occurs, the hearing loss is referred to as a mixed hearing loss.

Mixed hearing losses cause difficulty of both loudness and distortion. Since mixed losses combine the characteristics of conductive and sensorineural loss, the extent of each component will determine its implications. If the conductive component is significant, with very little damage to the nerves of the inner ear, the disorder will center on loudness rather than distortion of sound. If the conductive component is minimal, with the sensorineural component more significant, the loss may carry a larger distortion factor.

As conductive losses tend to fluctuate, depending on the nature of the loss, mixed losses may also fluctuate and the child’s response behavior could vary from day to day (13).

D. Auditory neuropathy/auditory dys-synchrony

Auditory neuropathy/auditory dys-synchrony (AN/AD) is a term presently used to describe a condition, found in some patients, in which the patient displays auditory characteristics consistent with normal outer hair cell function and abnormal neural function at the level of the VIIIth (vestibulo-cochlear) nerve.

With other words the inner ear or auditory nerve is unable to produce a synchronous response to incoming sound (14).

Possible sites of (AN/AD) include the inner hair cells, the tectorial membrane, the synaptic juncture between the inner hair cells, auditory neurons in the spiral ganglion, the VIIIth nerve fibers, or any combination. Neural problems may be axonal or demyelinating. Afferent as well as efferent pathways may be involved. The problem might also be related to a biochemical abnormality involving neurotransmitter release. AN/AD results in degraded processing of temporal cues in speech. Consequently, persons with AN/AD frequently experience inordinate difficulty understanding speech, especially in the presence of competing noise.

Recent reports have suggested that AN/AD is a relatively common cause of childhood hearing loss, with as many as 10%-15% of congenital hearing losses attributed to AN/AD (Rance, 2005). Consequently, it is likely that most pediatric audiologists have provided or will provide audiological services for a child with AN/AD. There is a contemporary assessment battery appropriate for identifying children with AN/AD (15).

IV. EARLY DETECTION METHODS

The importance of early detection and rehabilitation of infants with hearing impairment can not be overstated. Unfortunately, the average time between birth and the detection of congenital hearing loss is 2.5 years. The Joint Committee on Infant Hearing (Joint Committee on Infant Hearing, 2007) recommend that all newborns be screened for
hearing loss by 1 month of age, have diagnostic follow-up by 3 months, and receive appropriate intervention services by 6 months of age. The only way of detecting congenital deafness at this age is by neonatal screening (16).

A review of the evidence for universal newborn hearing screening shows that the technologies used (otoacoustic emission-OAE and automated auditory brainstem response-AABR testing) are accurate tests for detecting congenital hearing loss (17).

A. Otoacoustic emissions (OAE)

Otoacoustic emissions (discovered by Kemp in 1978) are narrowband acoustic signals generated by the inner ear of normal hearing individuals, either in the absence of acoustic stimulation (spontaneous emissions) or in response to acoustic stimulation (evoked emissions). These emissions can be detected by analyzing the signals obtained by placing a tiny microphone at the entrance to the ear canal, a procedure both simple and noninvasive. The mechanisms generating these emissions appear to be the same nonlinear feedback processes which responsible for the remarkable ability of the normally hearing individual to detect and analyze low level sounds. Most hearing impairment begins with a weakening or loss of this nonlinear feedback. Consequently, otoacoustic emissions potentially provide a useful clinical tool for the evaluation of inner ear function and diagnosis of hearing impairment (18).

B. Auditory brainstem response (ABR)

Auditory brainstem response (ABR) is a neurologic test of auditory brainstem function in response to auditory (click) stimuli. This measures not only the integrity of the inner ear, but also the auditory pathway. The stimulus (either clicks or tones) is presented using either earphones or an ear canal probe, and the electrophysiological response from the brainstem is detected by scalp electrodes (19).

The methods described do not assess hearing but rather are objective measures to estimate the likelihood of adequate hearing function. The combined method (OAE and ABR) is ideal for screening in any circumstances. They can be used for newborn hearing screening, to test infants and toddlers and also can be used for testing adults.

We have to underline that in AN/AD, the auditory brainstem response (ABR) is absent in most cases. In spite of the abnormal ABR, evidence of normal or near-normal outer hair cell (OHC) function exists as indicated by present otoacoustic emissions (OAE).

Because the incidence of AN/AD is higher for children who have had an extended stay in the neonatal intensive care unit (NICU), universal newborn hearing screening in the NICU must be conducted with an ABR—rather than OAE—screening (20). An OAE screening may provide a passing result and fail to identify the significant impairment of auditory function (21).

C. Other audiological test procedures

Behavioral audiometric assessment should also be conducted to determine the impact of the disorder on the child’s hearing sensitivity. Behavioral observation audiometry may be conducted during the first few months of life to look for evidence of responsiveness to sound, and visual reinforcement audiometry should be attempted at 6 months of age to determine behavioral thresholds.

Tympanometry – measures the middle-ear status. This test can be helpful in detecting fluid in the middle ear, negative middle ear pressure, disruption of the ossicles, tympanic membrane perforation, and otosclerosis.

Acoustic reflex testing consists of subjecting the ear to a loud sound and determining if it causes the stapedius muscle to tighten the stapes.

Audiometry - The goal of the audiologic evaluation can vary as a function of the age or developmental level of the child. The audiogram provides the fundamental description of hearing sensitivity. Typically, earphones are used and air-conducted signals are presented through them and are used to provide information regarding the sensitivity of the auditory system. Auditory steady-state response is a new evoked-potential test that can accurately measure auditory sensitivity beyond the limits of other test methods (22).

D. Early intervention methods

The early intervention for children with hearing loss in a nationwide problem in developed countries and determined governments to introduce universal newborn
hearing screening programs. Screening can be regarded as a specific intervention with the aim of detecting disease or certain health conditions in individuals who are not primary suspected of having them (23).

Prior to implementation of universal newborn hearing screening, testing was conducted only on infants who met the criteria of the high-risk register (HRR). It was found that the HRR was not enough, given that as many as 50% of infants born with hearing loss have no known risk factors (24).

The early intervention program

Newborn hearing screening should be completed by one month of age (or one month post discharge for babies who have been in the NICU), with ABR testing. If results are abnormal, the infant will be referred for diagnostic audiological evaluation. The goal is to provide audiologic diagnosis with ear specific information regarding degree, configuration, and type of hearing loss by three months of age (or three months post discharge for babies who have been in the NICU), and commence habilitation before six months of age.

A genetic consultation should be offered to the parents who’s infants hearing loss was confirmed. This evaluation can provide families with information on etiology of hearing loss, prognosis for progression, associated disorders (e.g. renal cardiac, vision). Once hearing loss is diagnosed in an infant, siblings who are at increased risk of hearing hearing loss should be referred for audiological evaluation (25).

Families should have access to information about all intervention and treatment options and counseling regarding hearing loss.

Early intervention services for infants with confirmed hearing loss should be provided by professionals with expertise in hearing loss, including educators, speech-language pathologists and audiologists.

Every infant with confirmed hearing loss should be evaluated by an otolaryngologist with knowledge of pediatric hearing loss and have at least 1 examination to assess visual acuity by an ophthalmologist.

The child and family should have immediate access to high-quality technology, including hearing aids, cochlear implants and other assistive devices when appropriate. Hearing-aid fitting proceeds optimally when the results of physiologic audiological assessment including ABR, OAE and tympanometry and medical examination are in accord. The goal of amplification-device fitting is to provide the infant with maximum access to all of the acoustic features of speech within an intensity range that is safe and comfortable (26).

Complementary or alternative technology, such as frequency modulation (FM) systems or cochlear implants, may be recommended as the primary and/or secondary listening device depending on the degree of the hearing loss, the goals of auditory habilitation and the infant’s acoustic environments (27).

The role of pediatrician/ primary care physician in monitoring children with hearing loss

The infant’s pediatrician or other primary health care physician is responsible for monitoring the general health, development and well-being of the infant. In addition, they must assume responsibility to ensure that the audiological assessment is conducted on infants who do not pass screening and must initiate referrals for medical specialty evaluations necessary to determine the etiology of the hearing loss. Because 30% to 40% of children with confirmed hearing loss have developmental delays the pediatrician or primary care physician should closely monitor developmental milestones and initiate referrals related to suspected disabilities (28).

CONCLUSION

1. Screening is one of the most important methods of early diagnosis of treatable diseases in children.
2. Hearing loss is one of the most common congenital anomalies, occurring in approximately 1-3 infants per 1000.
3. About 50% of infants born with hearing loss have no known risk factors.
4. Early identification and intervention of hearing loss can prevent severe psychosocial, educational, and linguistic repercussions.
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