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# CMV-induced Hearing Loss

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## Abstract

Congenital cytomegalovirus (cCMV) infection is the most common fetal viral infection and contributes to about 25% of childhood hearing loss by the age of 4 years. It is the leading nongenetic cause of sensorineural hearing loss (SNHL). Infants born to seroimmune mothers are not completely protected from SNHL, although the severity of their hearing loss may be milder than that seen in those whose mothers had a primary infection. Both direct cytopathic effects and localized inflammatory responses contribute to the pathogenesis of cytomegalovirus (CMV)-induced hearing loss. Hearing loss may be delayed onset, progressive or fluctuating in nature, and therefore, a significant proportion will be missed by universal newborn hearing screening (NHS) and warrants close monitoring of hearing function at least until 5–6 years of age. A multidisciplinary approach is required for the management of hearing loss. These children may need assistive hearing devices or cochlear implantation depending on the severity of their hearing loss. In addition, early intervention services such as speech or occupational therapy could help better communication, language, and social skill outcomes. Preventive measures to decrease intrauterine CMV transmission that have been evaluated include personal protective measures, passive immunoprophylaxis and valacyclovir treatment during pregnancy in mothers with primary CMV infection. Several vaccine candidates are currently in testing and one candidate vaccine in phase 3 trials. Until a CMV vaccine becomes available, behavioral and educational interventions may be the most effective strategy to prevent maternal CMV infection.



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**Keywords**

ABR thresholds; Auditory brainstem response and otoacoustic emissions; Aural preference syndrome; Behavioral audiometry; *Betaherpesvirus* ; Blood-labyrinth barrier; Cerebellar hypoplasia; Cerebral atrophy; CMV PCR; CMV-specific hyperimmune globulin; Cochlear blood–labyrinth barrier; Cochlear implant; Cytomegalic inclusion disease; Cytomegalovirus (CMV); Dried blood spot (DBS); Endocochlear potential; Fluctuating hearing loss; Ganciclovir; *Herpesviridae* ; Human Herpes Virus 5; Icosahedral capsid; Impedance audiometry; Intracranial calcifications; Lenticulostriate vasculopathy; MF59-adjuvanted CMV glycoprotein B subunit vaccine; Migrational abnormalities; Natural killer; Neurotrophins; Newborn hearing screening; Nlrp3; Non-primary maternal infection; Organ of corti; Periventricular echo density; Play audiometry; Pure tone audiometry; Sensorineural hearing loss (SNHL); Seroimmune; Speech audiometry; Spiral ganglion cells; Spiral ganglion cells; Spiral ganglion neurons; Strain-specific epitopes; *Stria vascularis* ; Tegument layer; Tympanometry; Unique long gene region; Unique short gene region; Valganciclovir; Ventricular adhesions; Ventricular dilatation; Ventriculomegaly; Viral core; Viral lipid bilayer envelope; Viral matrix; Viral replication cycle; Visual reinforcement audiometry; White matter disease

## Introduction

Congenital cytomegalovirus (cCMV) infection is the most common congenital infection with a birth prevalence reported around 0.64%.[1,2] Cytomegaloviruses are ubiquitous and the largest human viral pathogens with respect to genome size.[3–5] Morton and Nance estimated that cCMV contributes to 21% of all hearing loss at birth and 25% of childhood hearing loss by 4 years of age.[6] It is also a major cause of cognitive and neurologic deficits.[7]

## Viral Structure

Cytomegalovirus (CMV), also known as human herpes virus 5, is classified in the *Herpesviridae* family and based on its ability to infect leukocytes, as a *beta-herpes virus*.[3] It is a double-stranded DNA (dsDNA) virus. It is characterized by species specificity and a slow replication cycle, often taking as long as 24 hours to produce virus progeny in infected cells and several days to weeks to produce visible cytopathic effects in laboratory cell lines. There is an icosahedral capsid, a tegument layer, a dense core surrounded by an amorphous matrix, and a lipid bilayer envelope with glycoproteins. There is a large dsDNA genome with 230 kilobases, which is organized into unique long (UL) and unique short (US) gene regions with internal and terminal repeats to enable four isomeric forms of the virus.[8] Cytomegalovirus gene products are, by convention, designated by whether these are encoded by the UL or US segment, and are numbered from “left-to-right.”[9] Table 1 provides a detailed description of virus components.

Cytomegalovirus genome shows high diversity which is attributed to alternative splicing phenomena[9,10] and contains many genes that enable the virus to evade host immune responses. Naturally acquired immunity does not protect against reinfection, thereby posing challenges in developing an effective vaccine.

## Epidemiology

Congenital cytomegalovirus is the leading nongenetic cause of sensorineural hearing loss (SNHL), accounting for 6–30% of pediatric hearing loss.[36–41] In 1964, Medearis et al. described the association between cCMV and SNHL; they noted hearing impairment in more than 40% (2/5) of the survivors with disseminated cCMV, which was described as cytomegalic inclusion disease (CID).[42]

Cytomegalovirus transmission requires a close contact with body fluids. Infected infants and toddlers are the most important source of infection for women of child-bearing age.[43–45] Another common route of CMV transmission is via breast milk from seropositive mothers. Approximately, 85–90% of infants with cCMV have no clinical abnormalities at birth (asymptomatic cCMV), but 10–15% of these children go on to develop SNHL. Among children with symptomatic cCMV, 40–60% develop sequelae including SNHL, cognitive, motor, and vision deficits. In the United States, CMV contributes to 15–25% of childhood hearing loss.[46] Among infants with cCMV born to mothers with primary CMV infection during pregnancy, hearing loss and other neurologic sequelae are much more common in children whose mothers acquire primary infection in the first trimester as compared with later in pregnancy.[47–49] The incidence of SNHL in children with asymptomatic cCMV ranges between 6 and 25%[50–52] and 22–65% in those with symptomatic disease.[50]

The most important risk factors for SNHL are first trimester primary maternal infections, disseminated infection at birth, and neonatal imaging abnormalities. Other risk factors include using ototoxic drugs, longer NICU stay, fetal distress, and the need for mechanical ventilation during the neonatal period. These risk factors have been associated with SNHL independent of cCMV and therefore, are not very specific. However, the predictors of hearing loss in children with asymptomatic infection and those born following non-primary maternal infection are not known. Most infants with asymptomatic cCMV may not be recognized in a timely fashion because (a) there are no clinical findings at birth; (b) there is no routine screening for cCMV; and (c) it is difficult to collect saliva or urine samples after 2–3 weeks following birth.

In contrast to other congenital infections such as rubella and toxoplasmosis, the prevalence of cCMV increases with higher seroprevalence rates in the population. The incidence of studies from highly seropositive populations such as Brazil, India, and South Africa have demonstrated high prevalence of cCMV. The average prevalence of cCMV infections in high-income countries with low seroprevalence in women of child-bearing age is 0.64–0.7%, compared with 1–6% in resource-limited settings with high seroprevalence.[53–55] Although symptomatic cCMV was believed to occur exclusively following primary maternal infection, it is now clear that the frequency of symptomatic cCMV is similar in infected children born following both primary and non-primary maternal infections.[56] In addition, the frequency of SNHL in children with cCMV is also similar following primary and non-primary maternal infections. However, children with cCMV following primary maternal infection more frequently develop bilateral and more severe degree of SNHL than those born to mothers with non-primary maternal infection.

Both symptomatic and asymptomatic infants with cCMV shed virus in urine and saliva for prolonged periods, up to 6 years of age. Infants with symptomatic infections shed higher amounts of CMV in urine.[57] Some studies have suggested that higher blood CMV viral load may be a predictor of hearing loss,[57] but others have not confirmed these findings.[46,58,59] Noyola et al.[60] reported that hearing loss and progressive hearing loss was associated with a shorter period of CMV shedding. However, Rosenthal et al.[46] found that longer duration of viral shedding was associated with delayed onset hearing loss.[61]

In a prospective study of 14,000 unselected live-born infants spanning 10 years, the incidence of cCMV was noted as 0.53%, with 5.4% symptomatic cases.[62] Hearing loss was seen in 22% of the cCMV-infected infants (21% in asymptomatic and 33% in the symptomatic group). Hearing loss may deteriorate in two-third of symptomatic patients and in about 25% of children with asymptomatic cCMV.[63,64] Although the incidence of SNHL among infected children born to mothers with primary infection during pregnancy and those born to mothers with non-primary infection was similar, it has been suggested that bilateral and severe/profound loss occurs more often following maternal primary infection.[65] As we do not know the predictors of SNHL including progressive and severe/profound loss, current recommendations are to monitor all infected children with regular audiologic evaluations during early childhood, up to 4–6 years of age.[62] In a systematic review of 37 studies, the prevalence of cCMV in developed countries was estimated to be 0.58%. SNHL was noted in 12.6%, averaging around 1 out of 3 symptomatic children and 1 out of 10 asymptomatic children. Based on current data, 5 out of every 10,000 children born each year will develop cCMV-related hearing loss.[43] The degree of hearing loss is severe to profound in most affected children and in addition, many have a delayed onset, and progression of the deficit. Bilateral loss is more common among symptomatic children.

### The Risk of cCMV Varies Based on Geographical Regions and CMV Seroprevalence

Worldwide, cCMV infection affects 0.2–2.5% of all live-born neonates.[61,66] Higher prevalence of cCMV infection is seen in populations with higher CMV seroprevalence rates.[57–59,67–69] In the United States, northern Europe, and other industrialized countries, 40–60% of the population shows CMV seroprevalence. The prevalence of cCMV is 0.64–0.7%. In contrast, near-universal seroprevalence rates have been observed in developing countries and the cCMV rates between 1 and 6% have been reported in these populations.[55,70] Population-based studies in Sweden,[71] Canada,[61] and the United States[50,72] have noted SNHL in 9.3–17% of infants with cCMV infections.[65]

## Vertical Transmission

Cytomegalovirus-related hearing loss occurs following both primary (mother acquires the virus for the first-time during pregnancy) or non-primary maternal infection (seroimmune prior to pregnancy). In regions with high CMV, seroprevalence such as, Asia, South America, and Africa, most cCMV infections occur in children born to mothers with non-primary infections,[2] which is attributed to either reactivation of a latent virus or reinfection with new CMV strains. Although intrauterine transmission rate is higher in women with primary infections, vast majority of infected infants are born to mothers with non-primary

infections.[43] Although the rate of vertical transmission is higher in women who acquire primary infection at later gestations, the risk of symptomatic infection and long-term sequelae are higher when maternal infection occurs during early gestation.

Birth prevalence of cCMV is directly proportional to maternal seroprevalence. High rates of non-primary infections also lead to a higher birth prevalence on a population level despite the lower risk of vertical transmission. Higher rates of CMV reinfections as demonstrated by the acquisition of new serologic responses against strain-specific epitopes were observed in seropositive mothers with infected offspring.[73]

Most CMV-seropositive mothers (>90%) shed the virus in breast milk.[74] About 40–50% of exclusively breastfed infants of seropositive mothers acquire CMV infection during the first 4–6 months of life.[75,76] Although postnatal transmission of CMV via breastfeeding can lead to sepsis-like illness in very low birthweight infants, these children have not been noted to experience long-term sequelae that can be specifically attributed to CMV infections.

## Pathogenesis

The pathogenesis of SNHL in children with cCMV is not well defined. Both virus-mediated direct cytopathic effects and inner ear inflammatory responses likely contribute to CMV-induced hearing loss.[77] In infants with symptomatic cCMV involving the central nervous system, treatment with 6 weeks of ganciclovir may reduce the risk of hearing deterioration at 6 months and possibly at 1 year of age.[67] However, one follow-up study comparing 6 weeks vs 6 months of valganciclovir in children with symptomatic cCMV showed no improvement in hearing in the short term; there was a modest improvement in hearing and developmental outcomes in the longer term.[68] During early stages of infection and viremia, CMV enters the inner ear from blood (the most important pathway of infection) or through cochlear aqueduct from subarachnoid space, and causes disruption of microcirculation, tissue hyperplasia in the organ of Corti, and cellular damage with loss of spiral ganglion neurons (SGNs) and changes in the endocochlear potential (EP) (Flowchart 1). The immune response induced by CMV infections including the activation of NK cells and increased expression of proinflammatory cytokines disrupt the blood–labyrinth barrier (BLB).[69,78,79] As cochlear implantation can improve hearing in most children with CMV-related SNHL, the neural pathways may be intact in most patients. However, the outcome following cochlear implantation in children with cCMV-related SNHL is more variable compared with children with SNHL due to other causes.[80–83]

A major barrier in understanding the mechanisms of cCMV-induced SNHL is the lack of small animal models. Recently, a murine model has been described where newborn mice infected with murine CMV (MCMV) develop disseminated viral infections including in the cochlea. These pups develop hearing loss similar to that seen in human infants with cCMV.[84,85] Findings in this model include hematogenous spread of the virus, induction of inflammatory responses, and the loss of spiral ganglion cells leading to increased auditory brainstem response (ABR) thresholds.[80,84,86,87] Reactive oxygen species (ROS)-induced inflammation contributes to hearing loss.[78,88] Activation of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in the cochlea and SGN activates

caspase 1 with consequent release of IL-1 beta and IL-18.[89] Chemokines, such as CCL8, CXCL9, and CXCL10 contributed to tissue inflammation in pups with ABR thresholds >60 dB. The cytopathology in the Organ of Corti was not prominent, but there was notable loss of SGN; increased ABR thresholds suggest that hearing loss may result from lesions in the auditory system other than hair cell loss.[78] Although viral antigens have been found in the inner ear,[76,90–92] the lack of significant inner ear histopathology along with persistence of inflammation in cochlea of mice with hearing loss indicates that inflammatory response and not direct virus-mediated cytopathology may play an important role in CMV-associated hearing loss.

Survival and neurite extension of the SGN is dependent on afferent input and on expression of the neurotrophins, brain-derived neurotrophic factor (BDNF) and NT3.[84,86,87,93] The loss of cochlear nuclei neurons may result in the loss of afferent input during critical period(s) prior to the onset of hearing.[80–82] Postnatal days 5–11 have been described as a critical period in mice; the ablation of the cochlea after postnatal day 14 does not result in neuronal loss in cochlear nuclei due to the acquisition of survival (antiapoptotic) functions in these cells.[83,85,94]

The potential mechanisms of CMV-related hearing loss may include (a) direct viral cytopathic effects; (b) immune response and inflammation leading to loss of SGN cells; (c) disruption of the BLB with damage in the *stria vascularis*, which is essential for maintaining EP; and (d) involvement of central auditory centers.

### Direct Viral Cytopathic Effect

Early immune responses include activation of natural killer (NK) cells with increased expression of inflammatory cytokines and antibody-dependent cell-mediated cytotoxicity.[87,96]

### Immune Response and Inflammation

The *stria vascularis* (SV) is critical for regulating the unique electrolyte composition of the extracellular fluid within the Organ of Corti and to maintain the EP,[97,98] which is the driving force for the transduction current in auditory hair cells.[99] It is maintained by high potassium levels in the endolymph.[100] Inflammatory cells and viral seeding can disrupt the SV[99,101] and consequently, the potassium cycle and EP.[101]

### Disruption of Blood–Labyrinth Barrier Leading to Damage to the SV and Loss of EP

The cochlear BLB in the SV is paramount for the homeostasis of the cochlea.[102,103] Li et al. found higher BLB permeability following CMV infection due to disruption of the BLB, microcirculation, and the internal microenvironment.[69,85,104]

### Involvement of Central Auditory Centers

SGNs are the first level of neurons of the auditory system; they receive electrical signal input from cochlear hair cells and transmit to the cochlear nucleus and thereafter to the auditory cortex[105] Cytomegalovirus may induce apoptosis in SGN cells[106,107] by via altered

calcium homeostasis[81] or expression of Bax and Bcl-2.[106] Flowchart 1 summarizes the current understanding of the pathogenesis of CMV-induced hearing loss.

Viral reactivation and localized host inflammatory responses to reactivation might promote hearing loss as CMV, similar to other herpesviruses, establishes latency after primary infection.[60]

## Clinical Presentation

About 10% of all infants with cCMV are symptomatic, and may present with hepatosplenomegaly, petechial, or purpuric rashes, jaundice with conjugated hyperbilirubinema, and/or microcephaly. The outcomes following cCMV infections are highly variable; most children with symptomatic cCMV develop sequelae such as SNHL, cerebral palsy, neurodevelopmental delay, and loss of vision.[70] About 50% of symptomatic neonates develop SNHL, of which two-thirds have neurologic deficits.[41,53,108,109]

About 10–15% of infants with asymptomatic cCMV with SNHL show permanent sequelae. Among infants with symptomatic infection, intrauterine growth retardation and petechiae are associated with the development of hearing loss. However, further study is needed to identify predictors of hearing loss in children with asymptomatic cCMV. CMV-associated SNHL can be delayed onset, progressive and fluctuating in children with both symptomatic and asymptomatic cCMV.[51,110–113] About half of the children with asymptomatic cCMV and hearing loss have bilateral impairment.[43,114]

Most infants with cCMV are not identified at birth because of the absence of clinical findings and because a significant proportion experience delayed onset and/or progressive SNHL, who are not identified with newborn hearing screening (NHS). Therefore, several strategies are being considered so that infected infants can be monitored closely for hearing loss and provide early intervention to improve outcomes. These strategies include screening of all newborns for cCMV (universal CMV screening) or CMV testing of all infants who fail their NHS (targeted CMV screening). In the United States, several states have enacted legislation mandating targeted CMV screening, CMV education during pregnancy or both. Currently, two of these states (Minnesota and New York) have implemented universal newborn CMV screening. As predictors of SNHL are not known, especially those with asymptomatic cCMV, all infected children should be monitored for hearing loss at least every 6 months through the 1st 5–6 years of age. Early detection and intervention during critical stages of speech and language function improves outcomes in children with CMV-associated hearing loss. Both primary and non-primary maternal CMV infections can lead to symptomatic cCMV infection and SNHL.[2] Although bilateral hearing loss is commonly associated with speech delay and is present in almost half of the cCMV-infected infants, recent studies have shown the adverse impact of unilateral SNHL on overall development.[111,112]

### Delayed Onset, Progressive and Fluctuating Hearing Loss

Infants with cCMV can develop delayed onset and progressive SNHL during early childhood, which may continue to progress through adolescence.[41,61,115] The risk of

developing SNHL after 5 years of age may not differ from that in uninfected children. Overall, 2% of the patients with SNHL require cochlear implantation.[116]

Children with cCMV have a higher probability of not passing their NHS (5–6%) compared with uninfected children (1–2%). However, a considerable proportion of children with CMV-associated SNHL will be missed on NHS because of delayed onset hearing loss and in some infants with mild hearing impairment.[117] Definitions of hearing loss, maternal infection, and neonatal infection are provided in Tables 2 to 4, respectively.

## Diagnosis

### Maternal Infection

**Serological Testing—**The presence of CMV IgG antibodies during pregnancy in previously seronegative individuals (seroconversion) is definitive evidence of primary maternal CMV infection. However, early prenatal or preconceptional serum specimens are usually not available. Although the presence of CMV IgM antibodies indicates an acute infection, lower specificity of IgM assays and the presence of CMV IgM during reactivation or reinfection with a different virus makes the CMV IgM assays less reliable.[123] When both CMV IgG and IgM antibodies are present in a sample, IgG avidity testing could help differentiate between primary and non-primary maternal infection because affinity maturation of IgG antibodies usually takes several months after primary infection. The presence of IgM antibodies along with low-avidity IgG argues for a primary infection whereas high-avidity IgG suggests the likelihood of non-primary infections.[124,125]

### Diagnosis of Fetal Infection

**Ultrasound—**Ultrasonographic features of fetal CMV infection include echogenic bowel, fetal edema, hepatomegaly, periventricular echo density, ventricular dilatation, cerebellar hypoplasia, and overall growth retardation.[126] However, these findings are seen in less than 25% of cCMV-infected fetuses and may also be found in other intrauterine infections and fetal diseases.[127]

**Amniocentesis—**Amniotic fluid can be tested for CMV using virus culture and PCR to identify infected fetuses.[128] However, amniocentesis should be performed at least 6–7 weeks after primary maternal infection and after 20 weeks of gestation[108,129] because the appearance of viral particles in the amniotic fluid only occurs after the fetus begins to urinate. PCR using amniotic fluid is more sensitive (70–90%) than CMV cultures to diagnose fetal CMV infection.[130,131]

### Diagnosis of cCMV in the Newborn Period

Most newborn infants with cCMV shed large amounts of virus in saliva and urine. The presence of infectious viruses, viral antigens, or viral DNA in saliva or urine samples confirms the diagnosis of cCMV (Flowchart 2). Since a substantial proportion of infants acquire CMV either from intrapartum exposure or postnatally from breastfeeding, it is important to test urine or saliva samples collected from infants within the first 2–3 weeks after birth to distinguish cCMV from a postnatal CMV infection. Postnatal infections

can result in a sepsis-like syndrome in extremely premature infants and those with a primary immune deficiency such as severe combined immune deficiency. Postnatal CMV infection is not associated with long-term sequelae such as SNHL. Testing of newborn saliva samples using CMV PCR has been shown to be highly sensitive and specific.[132] To avoid contamination of saliva with CMV in breast milk from seropositive mothers, it is prudent to collect the saliva sample at least 90 minutes after breastfeeding. However, a large newborn screening study showed that false-positive saliva results are rare.[133]

As traditional culture methods are labor- and resource-intensive, and time-consuming, most clinical microbiology laboratories have phased out this test. In addition, culture-based assays are not suitable for screening large numbers of infants. In contrast, PCRs are less expensive with faster turn-around times, can be scaled up for high throughput capacity, and obviate the need to maintain tissue culture facilities. In addition, storage and transport conditions of samples usually does not affect the reliability of PCR results.[134–139]

### Dried Blood Spot (DBS)

Testing of DBSs collected at the time of newborn metabolic screening for CMV allows retrospective diagnosis in children presenting with clinical findings or sequelae consistent with cCMV. However, there are some limitations such as lower sensitivity of PCR using DBS. Therefore, DBS CMV PCR cannot be used for mass screening for cCMV. The test does show high specificity (>99.9%) and can be useful in some instances.

### Cranial Imaging

MRI brain can detect intracranial abnormalities in about a third of patients with probable or confirmed cCMV-induced SNHL. Brain ultrasound and/or MRI imaging findings in children with symptomatic cCMV include intracranial calcifications, migrational abnormalities, white matter disease, cerebral atrophy, ventriculomegaly, ventricular adhesions, and lenticulostriate vasculopathy.[140] However, many of these findings such as subependymal cysts and lenticulostriate vasculopathy are not as specific.

### Other Evaluations

Ophthalmologic evaluation should be done to rule out chorioretinitis, optic atrophy, or retinal hemorrhages. However, eye findings are infrequent in children with asymptomatic cCMV.

### Audiologic Evaluation

All newborns in the United States and most high-income countries undergo hearing screening prior to hospital discharge. More infants with cCMV fail NHS, about 5–6%, compared with 1–2% of uninfected children supporting the strategy that all babies who fail NHS should be tested for cCMV (hearing-targeted CMV screening). Although this approach identifies newborns with CMV-associated hearing loss but without clinical abnormalities, infected infants with asymptomatic cCMV who develop delayed onset hearing loss are not detected, arguing for universal newborn CMV screening. Cost-benefit analyses have shown that both hearing-targeted and universal CMV screening are cost-effective because identification of infants with cCMV and associated hearing loss will permit early

intervention such as hearing amplification including cochlear implantation, antiviral therapy, and other measures to improve outcomes.[141]

In 2013, Utah became the first state to enact a CMV public health initiative on CMV education[11] and mandating CMV testing of all infants who fail NHS for CMV.[1,75,142] Many other states have enacted legislations mandating education and/or universal CMV screening; Minnesota and New York have recently implemented Universal newborn CMV screening.

CMV-associated SNHL has wide variability with respect to the severity of the loss, laterality, the time of onset, and the type of loss. There is no characteristic audiogram pattern seen in SNHL due to cCMV. Considering that nearly half of all children with cCMV and SNHL pass their NHS,[118] and with the lack of predictors or biomarkers to identify those at increased risk for delayed onset and/or progressive SNHL, there is a need to monitor hearing function in all infected children closely during first 4–5 years of age.[50,62]

Newborn hearing screening is carried out using either otoacoustic emission testing (OAE) or an automated auditory brainstem evoked response (ABR). In children who fail NHS, hearing loss should be confirmed by full-scale diagnostic ABR but unfortunately, ABR testing beyond neonatal age may require sedation. Visual reinforcement audiometry (VRA) can be used as early as 7 months of after birth. Audiologic evaluation in older child is performed in a soundproof environment using pure tone audiometry, speech audiometry, behavioral audiometry, visual reinforcement audiometry, play audiometry, impedance audiometry, tympanometry, and/or electrophysiologic tests (including auditory brainstem response and otoacoustic emissions).

As with children with SNHL from other causes, children with CMV-associated hearing loss should also undergo genetic evaluation to identify the presence of an underlying genetic abnormality. Flowchart 2 describes the diagnostic algorithm for CMV-induced hearing loss.

## Treatment

### Antiviral Therapy

Ganciclovir and valganciclovir, nucleoside analogs, inhibit CMV replication by disrupting viral DNA synthesis.[143] A randomized controlled trial of intravenous ganciclovir for 6 weeks in infants with symptomatic cCMV with central nervous system involvement provided modest benefit by preventing progression of hearing loss and maintaining normal hearing. A subsequent study evaluated 6 weeks versus 6 months of oral valganciclovir therapy in children with symptomatic cCMV; although hearing and neurodevelopmental outcomes at 6 months were not different, the 6-month course showed significantly better outcomes at 1 and 2 years of age. Long-term follow-up studies still need to be performed and it is not known whether the benefits of antiviral therapy persist over time. The role of antiviral therapy in children with asymptomatic cCMV and those with mild symptomatic infection is not known and therefore, not recommended for these groups. Antiviral therapy is not recommended for preterm infants born those before 32 weeks of gestation because of the lack of pharmacokinetic data.[144]

Current guidelines for antiviral therapy in infants with moderate to severe symptomatic cCMV consists of a 6-month course of valganciclovir at 16 mg/kg/dose twice a day.[67] A complete blood count, transaminase levels, blood urea nitrogen (BUN) and creatinine should be done every 2–4 weeks during therapy. Children on treatment should be monitored for bone marrow suppression and in case of persistent neutropenia, valganciclovir should stopped temporarily. In addition, hepatic and renal function should be monitored.[73]

The management of cCMV-induced induced hearing loss has been summarized in Flowchart 3.

## Multidisciplinary Approach

Children with hearing loss should be managed by a multidisciplinary team including audiologists, otolaryngologists, speech pathologists, clinical geneticists, genetic counsellors, and educational specialists. An ophthalmologic evaluation should be completed in all infected children. They should be referred to an early intervention services to meet the needs of hearing-impaired children including preferential seating or frequency-modulated (FM) systems at school. In children with early hearing loss, interventions including hearing amplification before the age of six months improves language outcome.[145]

## Early Intervention Therapy

cCMV warrants periodic audiologic monitoring at 6-month intervals till 5 years of age, with frequent follow-ups 3 monthly when hearing levels are fluctuating. Frequent ear infections in young children lead to conductive hearing loss which superimposes SNHL leading to a delay in obtaining baseline audiologic data and requiring repeated follow-up assessments.

## Hearing Aids

In-the-ear and in-the-canal hearing aids are appropriate only for hearing loss less than 60 decibels (dB). Digital and programmable hearing aids have better sound quality, increased precision, improved speech recognition.[146,147]

## Assistive Listening Devices and Bone Conduction Hearing Devices

Bone-anchored implantable hearing aid system (BAHA) is feasible only in children 6 years of age or above because 3 to 4 mm of bone is needed to ensure osseointegration.[148]

## Cochlear Implantation

Implantation at an early age (“critical period” of hearing development) provides better outcomes with bilateral implantation providing improved sound localization and ability to understand speech in noisy surroundings.[114,149] These management strategies have been approved by the US Food and Drug Administration for use in children as young as 12 months, although off-label use can be done in infants <12 months old.[150]

Hearing aids are recommended for children with unilateral or bilateral SNHL ≥40 db HL, and cochlear implants for those with bilateral SNHL ≥70 db HL. Around 5% of children with asymptomatic congenital CMV infection have SNHL ≥70 dB HL in at least 1 ear by

age of 12 months, and half of these children meet current candidacy criteria for cochlear implantation.[116]

As we have not yet identified specific predictors of cCMV-induced SNHL, all infected children should be monitored with periodic audiologic evaluations to detect delayed onset and progressive hearing loss. Over 55% of the children will develop delayed onset loss occurring after the newborn period and 50% of all children with CMV-related SNHL will have progression or further deterioration of their loss overvtime.[50] In a prospective study conducted over 22 years, 5.7% of all cCMV-infected neonates ultimately required hearing amplification (hearing aid or cochlear implantation), with 44.4% of those with symptomatic infection and 3.4% of asymptomatic group requiring hearing rehabilitation.[140] Goderis et al. reported that there was a need for hearing amplification in 1.6% in children with asymptomatic and 29.3% in those with symptomatic infections.[151]

Unilateral hearing loss early in life can have deleterious effects on speech and language development and such children perform worse than their peers.[152,153] The term “aural preference syndrome” happens when a single-sided deafness in early childhood reorganizes the developing auditory pathways towards the hearing ear, with weaker central representation of the impaired side. Asymmetric hearing warrants a need for early, effective stimulation in both ears by appropriate fitting of auditory prostheses, including hearing aids and cochlear implants.[154]

Cytomegalovirus in blood is generally undetectable after one week of valganciclovir therapy. Continuous or intermittent detection of CMV at the age of 1 year has been seen in infants with SNHL. Cytomegalovirus load at diagnosis cannot predict the hearing outcome, but prolonged CMV viremia during treatment is a risk factor for SNHL and neurological sequelae.[155] Flowchart 3 demonstrates the management of CMV-induced hearing loss.

## Prevention

In seronegative pregnant women, behavioral and hygiene precautions were effective in preventing primary maternal CMV infection.[43] The effectiveness of CMV hyperimmune globulin (HIG) to prevent intrauterine transmission of CMV in primary maternal infection has been investigated. Although non-randomized cohort studies have shown that HIG can prevent intrauterine transmission in mothers with primary infection, this benefit was not confirmed in the two randomized placebo controlled clinical trials. Antiviral therapy with valacyclovir has shown promise in preventing intrauterine transmission in women with primary maternal infection.

### CMV Hyperimmune Globulin

Cytomegalovirus-specific HIG therapy of pregnant patients with primary CMV infection in early pregnancy has been studied to prevent or reduce cCMV in offspring. In spite of the fact that earlier non-randomized studies have shown the efficacy of CMV HIG prophylaxis in primary maternal infection, the two randomized trials did not decrease the rate of cCMV in the HIG group compared with the placebo group.[156,157]

### Vaccine Development

A report by the Institute of Medicine of the United States National Academy of Sciences designated that the development of a vaccine to prevent or reduce the adverse outcomes of cCMV is a priority.[158] Although a licensed CMV vaccine is not available, several candidate vaccines are currently in various stages of development.[159] In a phase 2 trial of an MF59-adjuvanted CMV glycoprotein B subunit vaccine in CMV seronegative women enrolled in the postpartum period, provided approximately 50% protection against acquiring primary infection.[160,161] However, the efficacy of the vaccine waned during the first 15 months of the study. The same vaccine given to seronegative teenagers failed to demonstrate protection from primary infection compared with placebo.[162] An mRNA-based vaccine expressing gB and the pentamer complex (mRNA-1647) examining the effectiveness of the candidate vaccine in preventing primary infection is currently in a phase 3 trial. A major challenge to the development of an effective vaccine is the fact that the majority of infants with cCMV are born to mothers with non-primary maternal infections. It is not known whether candidate vaccines that induce immune responses similar to those following natural infection will also provide protection against cCMV in infants born to seropositive women.

### Prevention of Hearing Loss in cCMV-infected Children

Newborn hearing screening identifies about 50% of all infants with cCMV infection who have hearing loss.[163] A majority of children with CMV-associated SNHL experience progression of the deficit during early childhood. Among infants with cCMV who pass their NHS, about 5% will have delayed onset loss during early childhood. In addition, predictors or biomarkers of progressive and delayed onset SNHL, especially in children with asymptomatic cCMV have not been defined. Therefore, hearing function of all infected children should be monitored at least every 6 months during the first 4–5 years age and annually thereafter to detect progressive and/or delayed onset SNHL.

A National Institutes of Health consensus panel and the Joint Committee on Infant Hearing have endorsed a goal of universal detection of infants with hearing loss by 3 months of age.[164] Cytomegalovirus screening should be made an integral part of NHS program to achieve early detection and confirmation of hearing loss by 3 months of age and interventions for those with SNHL should begin by 6 months of age.[11]

## Future Directions

Future efforts should be directed at elucidation of the mechanisms and pathogenesis of CMV-related hearing loss allowing for developing interventions to prevent or reduce this disability to develop support for newborn CMV screening programs, understanding the reasons for the failure of natural immunity to protect against reinfection/reactivation leading to cCMV, and the development of an effective vaccine to prevent or reduce the disease burden of cCMV including in highly seropositive populations and resource-limited settings.

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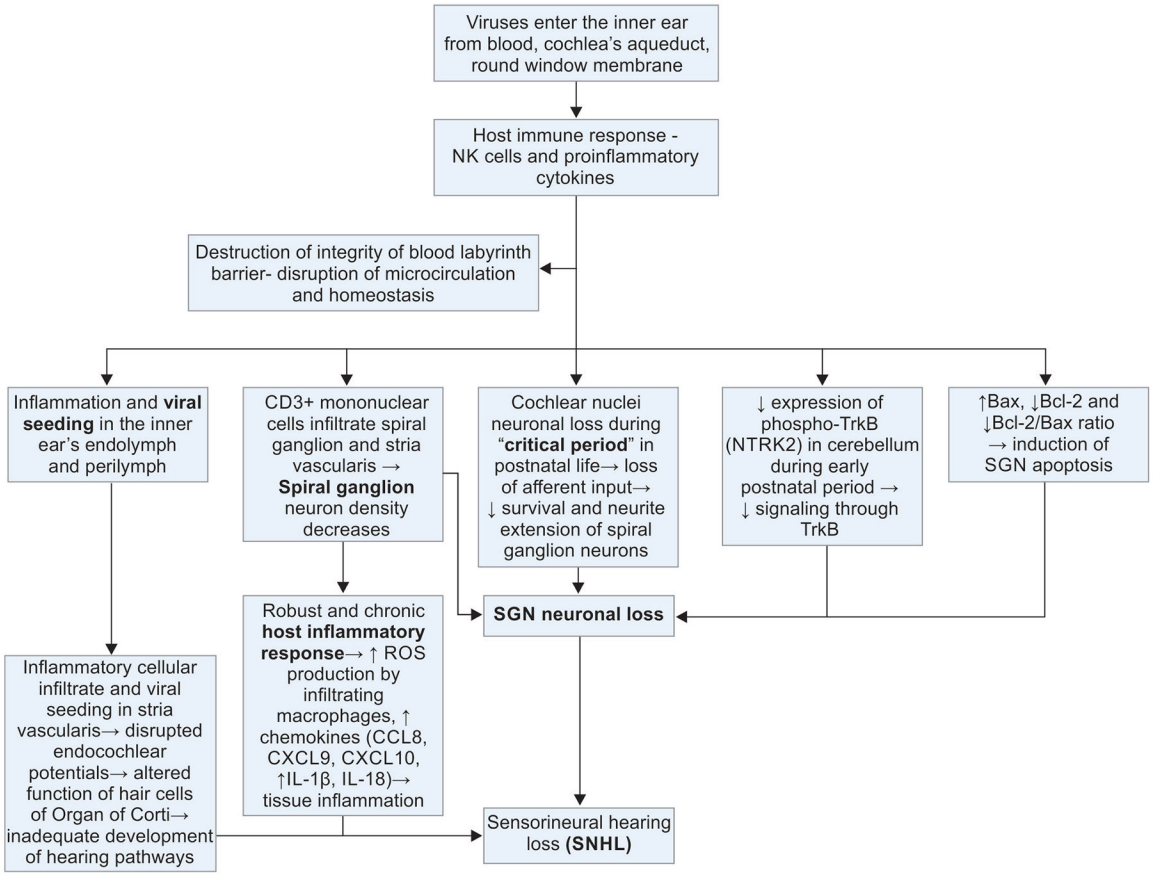
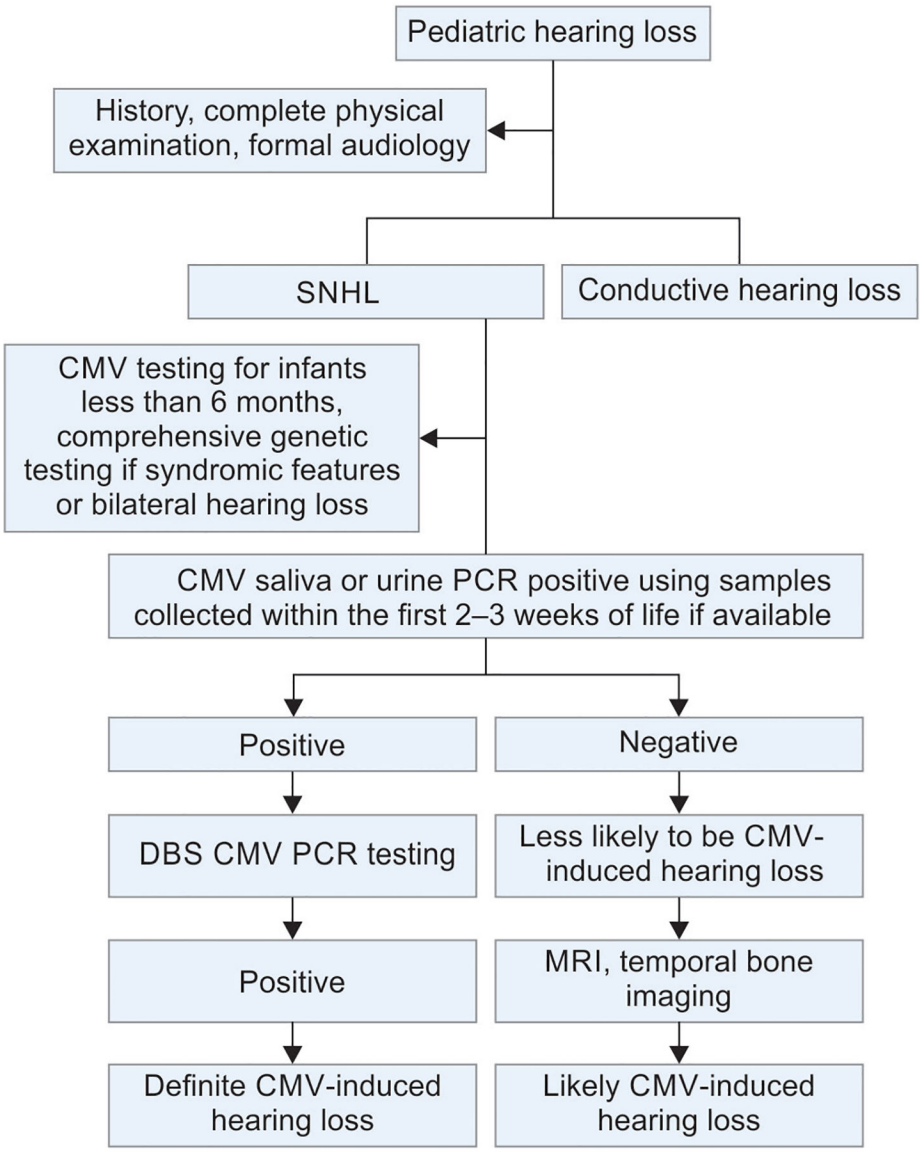
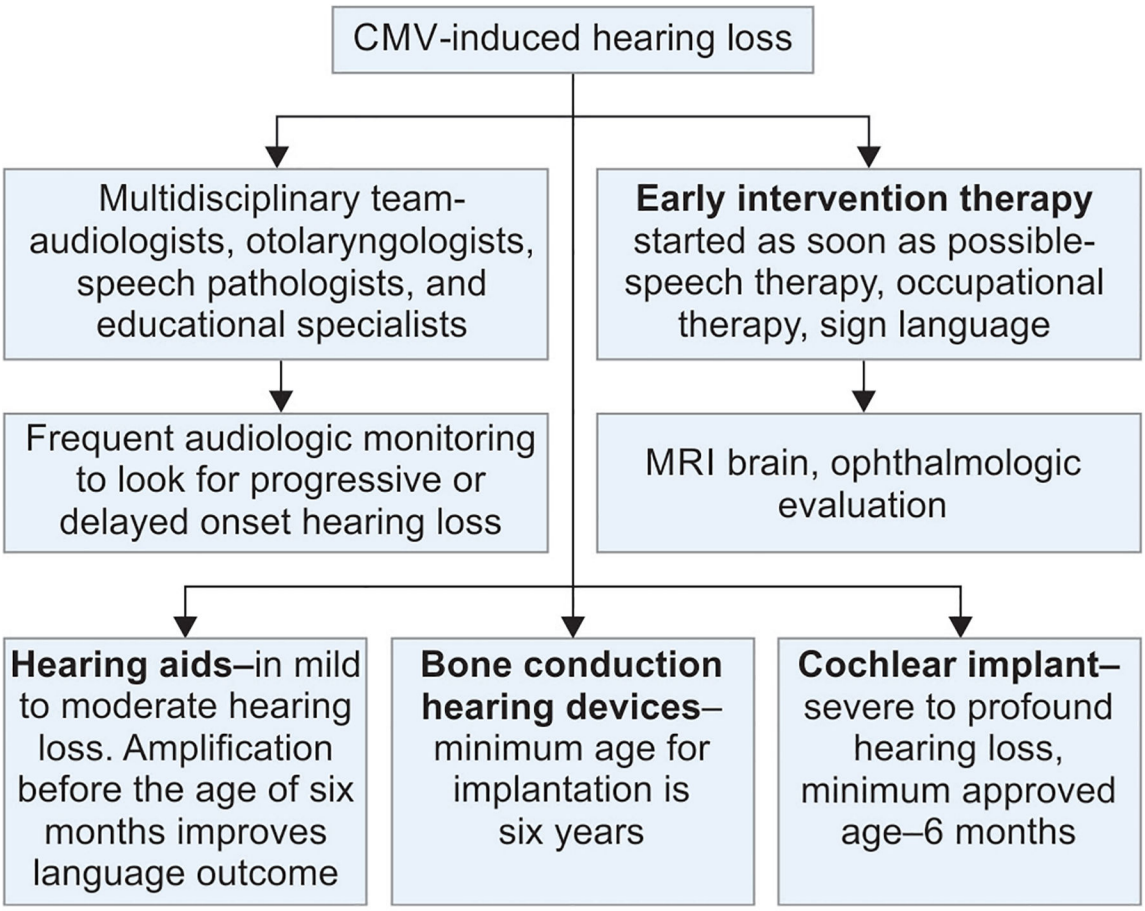



**Flowchart 1:**
Pathogenesis of CMV-induced hearing loss




**Flowchart 2:**
Diagnostic algorithm of CMV-induced hearing loss




**Flowchart 3:**
Management of CMV-induced hearing loss

**Table 1:**

Major structural components of CMV

| Structure | Available information |
|---|---|
| Lipid envelope | The lipoprotein envelope is derived from the nuclear membrane of an infected host cell and covers the nucleocapsid.[11] Cytomegalovirus has a characteristic three-layer architecture—an outer lipid bilayer envelope, inner nucleocapsid, and a middle tegument compartment |
| Glycoproteins | There are eight different glycoproteins embedded in the lipid bilayer.[11] Envelope surrounds the tegument and contains glycoproteins—the gB complex, the gM/gN complex, the gH/gL/gO "trimeric" complex, and the "pentameric complex" (PC) or pentamer comprising of proteins gH/gL/UL128, 130, and 131. Neutralizing antibodies targeting these glycoproteins are thought to be important component of protective immunity, hence recombinant forms of these proteins are candidates for vaccine development[12] |
| Receptor-binding motifs | Receptor-binding motifs are involved in virion attachment to host cell surface receptors during the process of infection and endocytosis. Cytomegalovirus utilizes binding to platelet-derived growth factor receptor alpha (PDGFRα) by glycoproteins gHgLgO (Trimer) and transforming growth factor beta receptor 3 (TGFβR3) to enter in multiple cell types.[13] The envelope proteins of the virus facilitate receptor binding by interacting with host cell proteins that act as binding factors and receptors—heparin sulfate proteoglycans (HSPGs), integrins, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), THY-1 cell surface antigen (CD90) neuropilin-2 (Nrp2), CD147, and OR14I1[14] |
| Envelope protein | The CMV envelope consists of various glycoprotein complexes that enable wide viral tropism[15] and facilitate attachment to cell surfaces and viral entry into the cells |
| Membrane protein | The human cytomegalovirus (HCMV) *UL50* gene encodes a transmembrane protein, pUL50, which acts as a core component of the nuclear egress complex (NEC) for nucleocapsids, which which facilitates capsid transport from the nucleus to the cytoplasm[16] |
| MHC or HLA proteins | Conserved B- and T-cell epitopes of CMV structural proteins may play an important role in evoking immune responses against CMV. Human-activated NK receptors also bind human CMV-encoded HLA class I-like molecules[17] |
| Spike protein | Glycoprotein gB is an elongated trimer and is similar to a spike with each protomer comprising 5 domains[18] |
| Viral tegument | In the mature virus particle, nucleocapsid is surrounded by tegument, a protein-rich layer containing several proteins which serve as targets of the host T lymphocyte response to infection, and hence are relevant to vaccine development. There is a high capsid pressure due to tightly packed, electrostatically repulsive genomic material in CMV, similar to HSV-1.[19,20] The β-herpesvirus–specific tegument protein pp150 contributes to a netlike tegument density layer stabilizing the capsid to facilitate the formation of infectious virions.[21–23] The tegument domain consists of approximately 30 proteins which play essential roles in the initial stages of infection following virus entry and late stages during virion assembly[24] |
| Capsid | Cytomegalovirus capsid has four parts—major capsid protein (MCP), triplex dimer (Tri2), triplex monomer (Tri1), and the small capsid protein (SCP).[25] Cytomegalovirus capsids have an icosahedral structure with major capsid protein (MCP) being organized in to 150 hexons and 11 penton vertices[26] |
| Capsomeres | Cytomegalovirus capsid has 162 capsomeres which function as structural subunits.[3] The capsid surrounds and encloses the viral dsDNA genome (forming a nucleocapsid) and can be seen as an electron-dense structure in electron micrographs |
| Protein core | There are 39 core proteins, which are present in all strains and are highly conserved.[27] Among the core proteins, some are involved in cell entry and immunomodulation/ immunoevasion; while the function of 17 of them (UL10, UL139 or US33A) has not been determined |
| Enzymes | Cytomegalovirus has an essential, maturational serine protease whose catalytic domain, assembling (28 kDa), is released by self-cleavage from a 74-kDa precursor (pPR, pUL80a)[28] |
| RNA elements | Cytomegalovirus encodes for 26 mature microRNAs (miRNAs) that regulate transcriptions of both virus and host cells and to favor viral infection and inhibit the host's immune response<br>Cytomegalovirus virion assembly involves the incorporation of RNA into infectious particles, which can be translated in newly infected cells in the absence of CMV genome transcription. It is also believed that nonspecifically incorporated cellular RNAs are crucial for virus assembly<br>Immediate early (IE) mRNA is transcribed within the first few hours after infection of the host cell and the encoded IE proteins, which include multiple isoforms due to extensive splicing, modulate both host and viral gene expression |
| Nucleosome | The human CMV genome does not carry histones when encapsidated but nucleosomes are formed after release into the host cell nucleus. Initial nucleosome formation is genetically encoded at the human CMV major immediate early (IE) locus, but as infection proceeds to the late phase, nucleosomes redistribute extensively[29] |

| Structure | Available information |
|---|---|
| DNA | Human cytomegalovirus has a double-stranded DNA genome of approximately 236 kbp containing >170 open reading frames (ORFs) encoding functional proteins.[30] The virus encodes approximately 200 genes, including nine gene families, a large number of glycoprotein genes, and homologues of the human HLA class I and G protein-coupled receptor genes[31] |
| Genome-associated polyprotein | CMV UL80 ORF encodes protease and assembly protein from its N- and C-terminal regions, respectively and a 30-kDa protease is derived by autoproteolytic processing of a polyprotein which is the translation product of the entire UL80 ORF[32] |
| DNA polymerase | During the early phase of CMV infection *in vitro*, the virus DNA polymerase is rapidly induced.[33] It has immunologic specificity and is the target of the three drugs, ganciclovir, foscarnet, and cidofovir[34] |
| RNA polymerase | CMV utilizes RNA polymerase II to transcribe viral genes and produce viral mRNAs. RNA polymerase I (Pol I)-mediated transcription is active in the nucleolus[35] |

HLA, human leukocyte antigens

**Table 2:**

Definitions of hearing loss

| Term | Definition |
|---|---|
| Conductive hearing loss | Hearing loss resulting from the disease process in the outer or middle ear that interferes with conduction of sound to the inner ear |
| Sensorineural hearing loss (SNHL) | Hearing loss due to damage, disease, or other disorders affecting the inner ear (eg., the cochlea) and/or the auditory nerve (cranial nerve VIII). Hearing loss is defined as sensorineural if the air-bone gap is <10 dB |
| Normal hearing | The ability to hear sounds between 0 and 20 dB |
| ABR threshold | The lowest intensity level at which wave V can be detected and replicated. An ABR click threshold >25 dB or a tone-pip threshold >30 dB is considered abnormal[118] |
| Mild hearing loss | Detection of sounds at 21–40 dB thresholds. A person with a mild hearing loss may hear some speech sounds but soft sounds are hard to hear[119] |
| Moderate hearing loss | Detection of sounds at 41–60 dB. A person with a moderate hearing loss may hear almost no speech when another person is talking at a normal level[119] |
| Severe hearing loss | Detection of sounds at 61–90 dB. A person with severe hearing loss will hear no speech of a person talking at a normal level and only some loud sounds[119] |
| Profound hearing loss | Detection of sounds only at 91 dB or greater. A person with a profound hearing loss will not hear any speech and is only able to hear very loud sounds[119] |
| Progressive SNHL | When children with SNHL either at birth or during early childhood experience a worsening of their hearing thresholds during later visits. (Deterioration in hearing of 10 dB or more at any 1 frequency on behavioral audiometry or ABR threshold, documented on two separate evaluations.[111,118] Fluctuating and progressive hearing losses are assigned only if there is no concurrent middle ear disease that might influence threshold variation |
| Fluctuating SNHL | A change to a worse or better hearing threshold between consecutive assessments: an absolute difference of ≥20 dB in ≥1 frequencies, ≥10 dB across any 2 or 3 adjacent frequencies, ≥10 dB in the average of the pure-tone thresholds at 0.5, 1, 2, and 4 kHz (4-frequency average), or a change from “hearing” to “no response” or vice versa at three adjacent frequencies.[116,120] |
| Improvement of hearing loss | Defined as a final threshold that is better by 10 dB or more compared with the initial threshold[26] |
| Stable SNHL | No change in hearing between two assessments |
| Late onset or delayed hearing loss | A child with normal hearing at birth, develops hearing loss at follow-up visits. Usually, there are one or more hearing evaluations with a normal threshold documented for each ear before detection of SNHL. |
| SNHL at isolated frequencies | Children with ≥25 dB hearing loss in any frequency without affecting the 4-frequency average |
| High-frequency hearing loss | A decrease in hearing at 4000, 8000, and 12,000 Hz frequencies only (or a combination of these).[111,118] |

* dB-Decibel

**Table 3:**

Definitions of maternal CMV infections[121]

| Term | Definitions |
|---|---|
| Primary infection | When a maternal seroconversion in a CMV IgG-negative individual occurs during pregnancy or when the serological results are highly suggestive of a primary CMV infection (positive IgM and low IgG avidity antibodies) |
| Presumptive primary infection | Some of the maternal CMV infections may have occurred in the months immediately prior to conception and CMV IgM antibody may last up to 3–6 months. Hence, they are considered presumptive primary infections |
| Proven primary maternal CMV infection | Mothers who were CMV IgG antibody negative during the first trimester of pregnancy, and did not have subsequent serologic testing, yet gave birth to a congenitally infected newborn, are considered to have a proven primary maternal CMV infection. Primary maternal CMV infections. Both proven primary and presumptive primary maternal CMV infections are grouped together as primary maternal CMV infections |
| Recurrent, or non-primary maternal CMV infection | When a congenitally infected neonate is born to a mother showing seroimmunity for CMV in a serum sample obtained before conception or when the serum sample obtained in the first trimester has high IgG avidity antibody. It is also defined as the presence of CMV IgG antibody before pregnancy, or presence of CMV IgG and absence of CMV IgM antibody during first trimester. Non-primary infections during pregnancy could be due to reactivation of mother's endogenous strain or reinfection with a new strain of CMV |
| Uninfected maternal status | Defined as mothers who are CMV IgG seronegative in the first trimester and remain CMV IgG seronegative throughout pregnancy, and deliver an uninfected newborn |
| Unknown type of maternal CMV infection | Defined as the presence of CMV IgG antibody and the absence of CMV IgM antibody in the mother at delivery. Mothers whose serologic data are either incomplete or unavailable are also included in this category |

**Table 4:**

Definitions of congenital/neonatal CMV infections[122]

| | |
|---|---|
| Congenital CMV infection | Cytomegalovirus infection acquired *in utero*. Diagnosis can be made within the first three weeks of life by detection of CMV in newborn's urine or saliva |
| Postnatal CMV infection | Cytomegalovirus infection acquired in the postnatal period. After three weeks, CMV detection in urine or saliva may indicate either congenital or postnatal CMV infection. Postnatal CMV infection usually is clinically benign or self-limited |
| Symptomatic cCMV disease | Defined as a newborn with CMV detected in urine or saliva samples collected within 3 weeks of life, presenting with at least one of the clinical findings at birth: purpura/petechiae, jaundice, hepatosplenomegaly, microcephaly, unexplained neurological abnormality, elevated liver enzymes (alanine aminotransferase >100 IU), conjugated hyperbilirubinemia (direct bilirubin >2mg/dL), or thrombocytopenia (platelet count <100,000/$mm^3$) |
| Asymptomatic cCMV infection | Defined as a newborn with CMV detected in urine or saliva samples collected within 3 weeks of life, who has a normal newborn examination, that is, none of the symptoms defining symptomatic cases |
| Primary neurophenotype | Refers to patients with only central nervous system manifestations. They lack the typical somatic manifestations and may appear completely healthy at birth or may have microcephaly. On follow-up, they develop neurologic manifestations and neuroimaging shows polymicrogyria or other cortical dysplasia |
| Asymptomatic with isolated hearing loss | Refers to infants with isolated hearing loss at birth but no other symptoms. Categorization of these infants as "symptomatic" or "asymptomatic" is inconsistent, hence considered as a distinct category because they are not truly asymptomatic, but their disease is milder than that of symptomatic infants |
| Virologically confirmed congenital CMV infection | Diagnosed on the basis of any of the following:<br>• Detection of CMV by viral culture in urine or saliva samples obtained within the first 3 weeks of life<br>• Detection of CMV by shell vial assay in urine or saliva samples obtained within the first 3 weeks of life, with a positive confirmatory test (viral culture or PCR)<br>• Detection of CMV via PCR in urine, saliva, or blood samples obtained within the first 3 weeks of life, confirmed on repeat testing<br>• Detection of CMV via PCR in the newborn screening dried blood spot |
| Possible congenital CMV infection | A diagnosis of "possible" congenital CMV infection may be made if all of the following criteria are met:<br>• One or more signs or symptoms of congenital CMV<br>• Other conditions that cause these abnormalities have been excluded<br>• Cytomegalovirus is detected in urine or saliva samples (via viral culture, shell vial assay, or PCR) or in the blood after the first three weeks of life |
| Not infected | Infants in whom CMV is not detected in urine or saliva (via viral culture, shell vial assay, or PCR) during the newborn period do not have congenital CMV. Because of the high sensitivity and specificity of these tests, a negative result excludes the diagnosis of congenital CMV infection. Congenital cytomegalovirus infection can be excluded beyond the newborn period if CMV IgG antibody testing is negative |