Congenital Infections and Hearing Loss: An Overview

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6.1 Introduction

Hearing loss (HL), defined as a partial or total loss of the ability to detect sound, can appear at any age and occurs when a part of the ear or auditory system has suffered a structural or functional deviation from the norm [1]. Three of the major categories of HL include (1) conductive: secondary to a mechanical concern preventing sound from traveling efficiently to the inner ear; (2) sensorineural: secondary to the inner ear or eighth cranial nerve damage); and (3) mixed: a combination of conductive and sensorineural [2]. Hearing loss can be mild to profound, may be unilateral or bilateral, and may be stable, progressive, or fluctuating.

Congenital HL is any hearing impairment identified at or shortly after birth and is typically sensorineural [3]. Congenital HL may be due to hereditary or nonhereditary causes, including congenital infections and ototoxic medications (Table 6.1) [4].

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Table 6.1 Leading causes of congenital and acquired sensorineural hearing loss

Congenital			
	Hereditary	Multiple syndromes	e.g., Alport, Pendred, Usher, and Waardenburg syndromes
	Nonhereditary		
		Congenital infections	Cytomegalovirus infection is the most common, and others include congenital toxoplasmosis, rubella, syphilis, and Zika virus infections
		Inner ear dysplasia or malformation	Ranges from mild to progressive
		Perilymph fistula	A leak of inner ear fluid through a defect in the otic capsule
Acquired			
	Prematurity	Perinatal complications, hyperbilirubinemia, noise, and ototoxic drugs increase the risk	
	Hyperbilirubinemia	The highest risk with levels above the threshold for exchange transfusion	
	Bacterial meningitis	Occurs early during the infection	
	Ototoxic drugs	e.g., aminoglycosides, high-dose loop diuretics, certain chemotherapeutic agents (cisplatin), salicylates, and antimalarial drugs	
	Noise exposure	Can occur over time with constant or repeated exposure	
	Trauma	Trauma to the temporal bone can cause sensorineural or mixed hearing loss	
	Tumor	Vestibular schwannoma occurs mostly in children with neurofibromatosis type 2	
	Heavy metals	Lead poisoning is the most common, but cadmium, mercury, and arsenic also may have toxic effects on cochlear cells	

Infections, including cytomegalovirus (CMV), rubella, Zika virus, lymphocytic choriomeningitis (LCMV), varicella-zoster virus (VZV), herpes simplex virus (HSV) infections, toxoplasmosis, and syphilis, transmitted to the fetus or newborn during pregnancy or childbirth may cause congenital HL [5]. The HL resulting from congenital infections may be identified at birth but is frequently progressive or delayed, emphasizing the need for universal newborn hearing screening (NHS) and continued close monitoring.

Congenital HL affects approximately 2–3 of every 1000 newborns in one or both ears [6]. The universal NHS in the United States of America (USA) in 2007 improved HL detection with earlier speech and language intervention [7–11]. Universal NHS programs have also been available in Canada, Europe, and most middle- and high-income countries [12]. Prevalence estimates are higher in countries where universal NHS programs are not implemented [13].

Many childhood HL cases can be detected right after birth through NHS. However, passing this test does not always lead to normal hearing. Thus, postnatal identification of HL will depend on later interactions and interventions [14].

The outcomes of HL, mainly if classified at a severe or profound degree, may include behavioral difficulties and learning and cognitive delays, and negatively affect the quality of life of children [15]. Therefore, early detection of HL and intervention are critical.

6.2 Pathophysiology

The pathophysiology leading to HL in viral infections is likely multifactorial. Inflammation may damage the cochlea, resulting in sensorineural HL (SNHL) [16]. A murine model study of HL induced in newborn mice infected with CMV found a significant inflammatory component [17]. Another study suggested that CMV infection (CMVI) associated with HL may be related to reactive oxygen species (ROS) induced inflammation [18]. Human CMVI increases ROS levels and activates inflammatory bodies of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in the cochlea [19]. A study with newborn mice infected with murine CMV reported virus-induced cochlear inflammation during auditory development instead of direct virus-cytopathic effects that might contribute to cochlea pathology and altered auditory function [20].

6.3 Infections

Congenital infections are among the primary causes of SNHL. Table 6.2 summarizes the general characteristics of leading congenital infections.

Table 6.2 The general characteristics of leading congenital infections

Infectious agent	Mode of acquisition	Transmission	Diagnosis (postnatal)	Clinical manifestations, in addition to sensorineural hearing loss
Toxoplasma gondii: Intracellular protozoan	Foodborne	Higher risk of transmission in later gestation More severe symptoms in earlier gestation	*T. gondii* specific IgG, IgM, and IgA, and PCR in blood and CSF	Intracranial calcifications, hydrocephalus, and chorioretinitis; asymptomatic >60% of cases
Rubella virus: RNA virus, Togaviridae family	Inhalation	Highest in the first trimester	Serum IgM and PCR in blood, nasopharyngeal swab, urine, and CSF	Cataracts, cardiac defects, microcephaly, and microphthalmia
Cytomegalovirus (CMV): DNA virus, Herpesviridae family	Bodily fluids	Transplacental	PCR in blood, urine, and saliva	Retinitis, intracranial calcifications, microcephaly, and mental retardation; asymptomatic in 85% of cases
Herpes simplex virus (HSV): DNA virus, Herpesviridae family	Bodily fluids	Intrapartum	HSV 1–2 PCR surface, blood, and CSF	Microcephaly, intracranial calcifications, skin, and ocular findings
Treponema pallidum: Spirochete	Sexual contact	Highest in the third trimester	Non-treponemal test in blood	Multiple organ systems and skin rash
Zika virus: Flaviviridae	Mosquito-born	Highest in the first and second trimesters	PCR in blood, urine, and CSF, serum IgM	Severe microcephaly, ocular, and cardiac abnormalities

CSF cerebrospinal fluid, *DNA* deoxyribonucleic acid, *Ig* immunoglobulin, *PCR* polymerase chain reaction, *RNA* ribonucleic acid

6.3.1 Congenital Cytomegalovirus Infection

6.3.1.1 Epidemiology

Congenital CMVI (cCMVI) is the most common intrauterine infection in children, with an incidence of approximately 0.5–1.3% and 40,000 new cases annually in the USA and 0.64–0.7% of neonates worldwide [21–24]. The prevalence varies among populations. It is estimated that cCMVI leads to about 13–22% of all cases of neonatal HL, making it one of the most common nonhereditary causes [25]. Congenital CMVI is also the primary cause of long-term neurological and sensory sequelae, the most common of which is SNHL [26]. Congenital CMVI-related HL is underestimated because most newborns are undiagnosed, which might be related to no

symptoms at birth and the absence of universal screening during pregnancy and childbirth in many countries [27].

The transmission risk is 30–35% and 1.1–1.7% for primary and non-primary maternal infection, respectively [25]. Even if 85–90% of newborns with cCMVI are asymptomatic at birth, 10–15% of these babies may develop hearing, visual, or developmental impairment [28]. Vestibular involvement may also result in delayed motor skills [29]. Cytomegalovirus infection was first identified as a cause of congenital HL in 1964 [30]. For almost 60 years, many studies have explored the relationship between cCMVI and HL. Currently, cCMVI is the most common acquired cause of childhood SNHL and neurodevelopmental problems [31]. The hearing impairment may be progressive and require cochlear implants eventually [32].

6.3.1.2 Clinical Manifestations and Diagnosis

Congenital CMVI can be asymptomatic, with isolated SNHL, and mild and moderate-severe symptomatic. Although 90% are asymptomatic, 7–21% of children with cCMVI can develop SNHL [33]. When symptomatic, cCMVI can be related to growth retardation, prematurity, microcephaly, chorioretinitis, seizures, and other neurological abnormalities. Mild symptomatic cCMVI is related to mild and transient symptoms. Moderate-severe symptomatic cCMVI is associated with multiple problems, including central nervous system (CNS) involvement. Moderate-severe cCMV disease in newborns causes involvement of CNS, such as microcephaly, cortical malformations, ventriculomegaly, periventricular calcifications, germinal cysts, SNHL, chorioretinitis, and systemic manifestations, including hepatosplenomegaly, transaminitis, direct hyperbilirubinemia, petechiae, thrombocytopenia, and intrauterine growth retardation (IUGR).

Neonates with SNHL without any other clinical manifestations are considered a subgroup of asymptomatic infection. About 5–15% of newborns with cCMVI asymptomatic at birth may develop SNHL as late-onset sequelae [34]. In a systematic review, neonates with asymptomatic cCMVI were less likely to have delayed-onset SNHL than symptomatic cases [35].

Sensorineural HL occurs in 6–25% and 20–65% of infants with asymptomatic and symptomatic cCMVI, respectively [33, 36]. Hearing loss in cCMV-infected newborns rarely improves over time, and most asymptomatic and symptomatic children ultimately have loss progression [37]. Risk factors for SHNL were reported as primary CMVI before the 14th week of pregnancy, disseminated disease, and imaging abnormalities in the newborn in a prospective 22-year study [38]. Genetic causes should also be investigated in infants with asymptomatic cCMVI and isolated HL [39]. Early treatment with antiviral therapy has improved hearing outcomes for neonates with cCMVI.

Despite extensive research, no clinical or laboratory evidence to identify the disease has been found in children with CMV infection. A study of infants infected congenitally using viral whole-genome next-generation sequencing (NGS) found genes and variants that might be related to symptomatic and HL outcomes, representing an important step in understanding the impact of disease on CMV genetic

variation. These studies also identified potential markers in infants with cCMV at increased risk for adverse outcomes [40].

Universal screening programs may identify some asymptomatic newborns. Based on abnormal screening, a study identified 75% of infants with cCMVI [41]. Since there are no outcome predictors for asymptomatic neonates with cCMVI, future studies are needed to evaluate targeted or UNHS to identify children at risk for SNHL [42].

6.3.1.3 Treatment

In a study of 76 children with cCMVI followed through 18 years of age, SNHL, severe enough to require a cochlear implant, developed in most symptomatic patients treated with or without 6-week ganciclovir therapy [43].

A systematic review revealed that valganciclovir and ganciclovir use significantly improved hearing improvement and resulted in less deterioration for children with cCMV-related HL at birth [44]. However, there was insufficient evidence of the potential benefit on the hearing outcome of children with isolated HL, late-onset HL, and asymptomatic cCMVI.

In a multicenter, nonblinded, non–placebo-controlled randomized study, the antiviral treatment of cCMV-associated SNHL progression was evaluated [45]. The neonates with CNS disease and SNHL were randomized to get either 6 weeks of intravenous (IV) ganciclovir or no treatment. Treatment with ganciclovir resulted in hearing improvement or preservation at 6 months and most likely at 1 year. In a recently published study by Lanzieri et al. [43], the initial benefits of 6 weeks of IV ganciclovir in severely affected children with cCMV disease and HL on HL progression were shown not to be long-lasting through childhood.

Another nonblind, non-placebo-controlled study randomized the ganciclovir treatment in asymptomatic neonates who tested positive for cCMVI after birth [46]. Twenty-three neonates with cCMVI were randomized to receive either IV ganciclovir for 3 weeks or no therapy. At the follow-up, 2 children (18%) and none developed SNHL in the control and treatment groups, respectively.

Later, a multicenter, blinded, placebo-controlled randomized study compared 6-week and 6-month courses of valganciclovir [47]. In the trial, oral valganciclovir was given to all neonates for 6 weeks and then randomized to either receive a placebo or continue to receive valganciclovir for 6 months. Those in the 6-month treatment group had a higher hearing preservation rate at 12 and 24 months. However, the study could not examine the effect of valganciclovir treatment in isolated SNHL, which only one neonate had.

In 2017, a consensus statement was declared by the International Congenital Cytomegalovirus Recommendations Group [48]. In this statement, for neonates with moderate or severe cCMVI, oral valganciclovir for a 6-month course was recommended. Routine antivirals for neonates with mild disease or SNHL are not recommended since there is a lack of clear evidence of preserved or improved hearing with the treatment. There is a concern because of the risks associated with prolonged antiviral treatment. Also, recent data show that the initial short-term benefits

observed in randomized controlled trials are not long-lasting for progressive, long-term HL in cCMV disease after gancyclovir therapy [43].

Laboratory monitoring is vital in infants being treated with valganciclovir since the treatment may result in neutropenia. Absolute neutrophil counts should be followed weekly for at least 6–8 weeks, then monthly for the duration of therapy.

Treatment and monitoring of cCMVI are complicated and require a coordinated, team-based approach, including multiple specialists in pediatric infectious diseases, ophthalmology, audiology, otolaryngology, neurology, developmental pediatrics, occupational and physical therapy, orthopedic surgeons, and physical medicine and rehabilitation. Hearing aids, cochlear implantation, and speech/language therapies also may benefit children with cCMV-associated HL.

6.3.1.4 Outcome and Prevention

Most recently, a retrospective observational study evaluated 59 neonates with isolated SNHL [49]. Neonates received 12 months of antiviral treatment, either 6 weeks of IV ganciclovir followed by oral valganciclovir or only oral valganciclovir. At follow-up, 68.8% of affected ears showed an improvement, whereas 2.5% experienced worsening hearing. Of the improved ears, 96.3% improved to have normal hearing. Improvement in hearing was more likely to be seen in mild to moderate HL than in severe HL. No difference was found in hearing outcomes between neonates who initially received IV therapy and those receiving only oral therapy.

Antiviral treatment has been shown to improve hearing outcomes in neonates with symptomatic cCMVI and central nervous system involvement [50]. Limited studies suggest that antiviral therapy improves or preserves hearing in children with isolated SNHL [51].

It is recommended to have hearing evaluations every 3–6 months during the first 3 years of life and annually until 18 years of age since the HL with cCMVI is progressive [52]. In children with cCMVI-related HL, middle ear effusions can complicate the problem. Early referral for evaluation and possible tympanostomy tube placement will improve the outcomes. Also, monitoring individual hearing thresholds in both ears is essential for appropriate interventions [53]. Cochlear implantation (CI) has been an effective rehabilitation method for patients with severe-to-profound HL. However, the outcomes vary depending on the degree, onset, progression, and duration of the HL [54].

Since cCMVIs, asymptomatic and symptomatic, cause sequelae risk, there is a necessity for universal and targeted newborn screening, identifying more infants with infection. Passing hearing screening does not always exclude HL because of the possibility of late-onset and progressive HL in children with cCMVI. Close audiologic follow-up is required because of the process resulting in HL due to cCMVI [55].

For newborns who fail the neonatal hearing test, a targeted screening has been started in some states and hospitals in the USA, even if there is no universal screening. Also, multiple bills have been passed recently that require state health departments to provide educational resources, targeting healthcare providers and young

women of childbearing age. Such programs may facilitate timely diagnosis and early intervention [56].

Ultimately, the prevention of cCMVI most likely requires the development and implementation of effective vaccination. Investigations of several vaccines have been in phase I and II human studies; however, many questions remain about using the CMV vaccine in clinical practice [57]. One candidate is a purified, adjuvanted recombinant vaccine against the immunodominant glycoprotein B present in the CMV viral envelope that has demonstrated promising results in preventing primary CMVI in young women [58].

6.3.2 Congenital Toxoplasmosis

Toxoplasmosis is caused by congenital or acquired infection of the parasite *Toxoplasma gondii.* Congenital toxoplasmosis is a significant cause of morbidity and mortality in fetuses, neonates, and children, related to vertical transmission from infected mothers. Most newborns with congenital toxoplasmosis are asymptomatic, but 10–30% might have clinical symptoms and signs at birth or early infancy [59]. Severe symptomatic infection usually results from primary maternal infection during the first trimester. The classic triad of congenital toxoplasmosis, chorioretinitis, hydrocephalus, and intracranial calcifications, occurs in <10% of the cases [60].

Hearing loss is reported in about 20% of congenital toxoplasmosis [61]. All newborns with suspected congenital toxoplasmosis should be evaluated for HL [62].

There is evidence of risk for hearing impairment with congenital toxoplasmosis [63]. However, the details of the hearing outcomes are still unclear, and the assessment and follow-up details have not yet been validated.

6.3.3 Congenital Rubella

Rubella virus, a single-stranded RNA virus from the family of Matonaviridae, genus Rubivirus, causes congenital or acquired infection. Congenital rubella infection (CRI) may lead to fetal death in utero, preterm delivery, intrauterine growth retardation, or congenital abnormalities. Congenital rubella infection is also called congenital rubella syndrome (CRS) when it results in severe congenital anomalies, including microcephaly, congenital heart disease, SNHL, and eye problems, such as microphthalmia, cataracts, and glaucoma [64]. Hearing loss, cataracts, and cardiac disease are the classic manifestations of CRS; however, the rubella virus may infect every fetal organ and persist for a long time. Most infants with CRI are asymptomatic at birth but develop symptoms over time [65].

Nearly two-thirds of children with CRI have SNHL, usually bilaterally [64]. Once the most common viral cause of congenital SNHL, CRI is now rare due to maternal vaccination programs in high-income countries and was eliminated from the USA and Americas region in 2015 [66, 67].

The Pan American Health Organization (PAHO) called for rubella and congenital rubella syndrome (CRS) elimination in the Americas by 2010 in 2003. In 2015, the Americas were declared free of endemic rubella and CRS. The Americas region has sustained the elimination of rubella and CRS until now.

The last endemic rubella case in the PAHO region was documented in 2009 [68, 69]. In other parts of the world, rubella control is improving through the widespread implementation of vaccine programs.

6.3.4 Congenital Syphilis

Congenital syphilis occurs when the spirochete *Treponema pallidum* is transmitted to a fetus through the transplacental transmission of spirochetes in the bloodstream or, occasionally, through direct contact with an infectious lesion during birth. Transplacental transmission can occur at any time but more as gestation advances. Many cases are asymptomatic at birth [70]. Typical findings in symptomatic infants include nasal discharge, jaundice, hepatomegaly, rash, lymphadenopathy, and skeletal abnormalities. Rarely, it can also cause sepsis, myocarditis, pneumonia, eye involvement, and central nervous system infection. Infants with proven and probable diseases should be treated with penicillin [71].

Congenital syphilis has decreased for decades and is still very uncommon, but it is, unfortunately, rising [72]. Most cases are related to mothers who had no prenatal care or insufficient treatment for syphilis before or during pregnancy [73].

Sensorineural HL could be a late manifestation of congenital syphilis, typically developing at the ages of 8–10 [74]. Newborns with positive syphilis serology at birth should have hearing screening performed and should receive treatment with an appropriate course of penicillin therapy, preferably before 3 months of age. For all patients with congenital syphilis, close hearing screening is recommended. Sensorineural HL associated with late congenital syphilis typically develops suddenly by 10 years of age; often, the patient has interstitial keratitis and may respond to long-term glucocorticoid therapy [75].

6.3.5 Congenital Zika Virus Infection

Zika virus is an arthropod-borne flavivirus transmitted by mosquitos. Congenital Zika virus is associated with fetal growth restriction and sequelae related to the central nervous system. The Zika virus epidemic in the Americas was first recognized in 2015 and caused significant consequences during pregnancy resulting in congenital microcephaly and auditory changes [76]. The risk for vertical transmission exists throughout pregnancy; however, the most important risk of severe fetal sequelae appears to be first- and second-trimester infection. Fetal loss occurs in approximately 5–10% of pregnancies with documented Zika virus infection [77]. There is no specific treatment for the Zika virus infection, and management is supportive [78].

Little is known about HL in infants with congenital Zika virus infection, even though HL related to other congenital viral infections is well described. Of 70 children with microcephaly and evidence of congenital Zika virus infection, 5.8% were found to have SNHL [76]. Including the infants appearing normal at birth, all infants born to women with any evidence of Zika virus infection during pregnancy should have hearing testing [79]. In a report of infants with in-utero Zika virus exposure, who were prospectively followed, the overall rate of hearing impairment was 12% [80]. Hearing loss with delayed onset has not been reported. Further research is needed to evaluate whether the virus can cause HL later during infancy or childhood [81].

6.3.6 Congenital Lymphocytic Choriomeningitis Virus Infection

Lymphocytic choriomeningitis virus (LCMV), a member of the Arenaviridae family, is a single-stranded RNA virus. Ordinary house mice and other rodents, including rats, hamsters, the primary hosts, and reservoirs, carry and shed the LCMV in their saliva, urine, or feces. Humans acquire the virus by ingesting contaminated material, exposure to open wounds, or inhaling aerosols [82]. The LCMV infections are usually asymptomatic or characterized by upper respiratory tract infection symptoms.

Lymphocytic choriomeningitis virus is a rare cause of congenital infections and is generally underdiagnosed. Transmission to the fetus occurs with maternal viremia and can damage the developing brain. The fetus may be affected by LCMV infection, mainly if maternal infection occurs during the first or second trimester of pregnancy [83].

Congenital LCMV infection is associated with a high mortality rate. Survivors may have microcephaly (or macrocephaly), hydrocephaly, periventricular calcifications, cerebellar hypoplasia, ventriculomegaly, chorioretinitis, pachygyria, seizures, and neurodevelopmental sequelae, including intellectual disability and HL [83–85]. Minimal data exist about the prevalence of HL associated with congenital LCMV infection. Microcephaly and visual impairment are more common than HL in congenital LCMV infection [86]. No vaccine or effective treatment is available. Avoiding mice and hamsters during pregnancy can reduce the infection risk [83, 87].

6.3.7 Neonatal Herpes Simplex Virus Infection

Neonatal herpes simplex virus (HSV) infection caused by HSV-1 and HSV-2 incidence is estimated to be about 10 in 100,000 live births [88]. Transmission usually occurs during delivery from mothers with herpes simplex virus type 1 (HSV-1) or HSV-2 genital infection.

In most cases, the infection presents in the first 3 weeks of life with disseminated disease, encephalitis, or localized infection. Neurologic impairment, including HL, is found in most children with disseminated infection [89], 40% with encephalitis, and 25% with disease confined to the skin, mouth, or eyes [90].

Intrauterine or congenital HSV infection is rare and results from either maternal viremia with primary HSV infection or ascending infection during pregnancy. The development of SNHL in children with neonatal HSV infection occurs rarely, mostly seen with disseminated disease [91]. Hearing loss related to the neonatal infection can be severe to profound SNHL, bilateral or unilateral [92]. One study evaluated four children with mild to moderate SNHL after herpes encephalitis [93].

6.4 Conclusion

Hearing loss is common in congenital infections. Considering the natural process of HL with congenital infections, frequent audiologic follow-up is required. Universal screening should be considered because many children might have delayed HL after congenital infections. National hearing screening programs in different parts of the world vary considerably in quality, data acquisition, and accessibility of services [94].

Targeted screening of newborns for cCMVI is getting growing interest in conjunction with UNHS. The evolution of newborn screening and potentially effective vaccine efforts to prevent CMVI is promising with increased awareness.

Early identification can assist with prognosis and counseling families for all congenital infections. Frequent audiologic follow-up and universal screening will detect asymptomatic children at birth who may develop late-onset or delayed HL. A coordinated approach to diagnosis, treatment, and monitoring for HL is required for better outcomes. Cochlear implantation effectively improves speech and language in kids with HL related to congenital infections.

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