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HEARING LOSS IN CHILDREN (D HORN AND H OU, SECTION EDITORS)

Management of Congenital Cytomegalovirus-Related Hearing Loss

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Abstract

Purpose of Review The aim of this report is to review the current literature regarding the diagnosis, treatment, management, and rehabilitation of congenital cytomegalovirus (cCMV)–associated sensorineural hearing loss (SNHL).

Recent Findings Hearing-targeted CMV screening is successful in identifying cases of cCMV-related hearing loss. However, a significant number of children who develop cCMV-related SNHL may not be detected on newborn hearing screening, and it may be cost-effective to implement a universal CMV screening program. We also broadly review the management and audiologic rehabilitation of cCMV-associated hearing loss, including cochlear implantation.

Summary Congenital CMV is a common cause of childhood SNHL. CMV testing is important for the workup and management of unknown SNHL. Antiviral therapies are currently only indicated in those with symptomatic cCMV infection and is currently under investigation in children with isolated SNHL. Hearing status is closely followed, and rehabilitation strategies are similar to other etiologies of congenital SNHL, and may include hearing amplification, speech therapy, and cochlear implantation.

Keywords Congenital hearing loss · Cytomegalovirus · Cochlear implantation · Sensorineural hearing loss

Introduction

Congenital cytomegalovirus (cCMV) infection is the most common intrauterine infection in humans. The global seroprevalence of CMV is estimated to be 83% in the general population and 86% in women of reproductive age. In the Americas, the seroprevalence rates in those groups are estimated to be 75% and 79%, respectively [1]. It is associated with many congenital conditions, including microcephaly, chorioretinitis, cognitive impairment, and/or cerebral palsy [2, 3]. Sensorineural hearing loss (SNHL) is the most common sequela of cCMV infection, with approximately half of symptomatic infants and 10–15% of otherwise asymptomatic cCMV infants developing SNHL. For otolaryngologists, cCMV infection is of particular importance, because it is the most common cause of non-genetic SNHL in young children, accounting for 21% of all SNHL at birth and 25% at 4 years of age [2, 4]. Here, we discuss the role of CMV testing in the workup of childhood SNHL, screening newborns for cCMV, and the audiologic evaluation and rehabilitation of cCMV-associated SNHL.

Audiologic Characteristics

Hearing loss in children affected by cCMV infection is sensorineural in nature, and a small study found that the most common audiologic configuration is a flat SNHL, with less than 10 dB difference across all frequencies [5]. The risk factors closely associated for developing hearing loss in infants with cCMV include symptomatic infection at birth, high viral load, and delayed intrauterine growth [6, 7]. A 10-year prospective study showed that 74/14,021 (0.53%) of all infants screened had cCMV infection, and overall 22% of those infected developed SNHL. This proportion was higher in the symptomatic cCMV group compared with the asymptomatic group (33% versus 21%). Over a 5-year follow-up period, late-onset hearing loss occurred in 5%, progression in 11%, fluctuation in 16%, and improved hearing in 18% of infants with cCMV infection [8]. A second long-term case-control

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study found that by age 18, the prevalence of SNHL in cCMV-infected patients was 25% (95% CI 17–36%) compared with 8% in the control group, with a prevalence of severe to profound bilateral SNHL in cCMV patients of 2% (95% CI 1–9%). Sixty-five percent of children with SNHL had progression of hearing loss, and 75% of children born with unilateral hearing loss ultimately developed hearing loss in the contralateral ear. After 5 years of age, the risk of delayed-onset SNHL was no different between cCMV-infected individuals and controls, suggesting that routine audiologic screening can be resumed at that point [9•].

Role of CMV Testing in the Etiologic Workup for Sensorineural Hearing Loss

In the USA, universal newborn screening has been implemented in many states with the support of Congress, federal agencies, and advocacy group through the development of state-run early hearing detection and intervention (EHDI) programs. Guidelines from the 2017 Position Statement from the Joint Committee on Infant Hearing (JCIH) recommend the following milestones: hearing screening by 1 month of age, comprehensive audiologic evaluation by 3 months for those who refer on screening, and medical evaluation by 6 months for those who have confirmed hearing loss [10]. As a part of the medical evaluation, which consists of a complete history, physical exam, and review of available audiologic testing, the otolaryngologist may consider whether additional diagnostic testing is indicated to determine the underlying etiology. For children without suspicion for syndromic SNHL, these tests may include imaging, genetic testing, and CMV testing [11]. The role of testing for cCMV has been proposed as a part of etiologic testing algorithms for non-syndromic SNHL [12–14]. Timing and type of testing for cCMV vary critically by age, and will be reviewed in detail in the next section.

Congenital CMV Testing

Neonatal Period

Viral culture or polymerase chain reaction (PCR) of urine or saliva obtained during the first 3 weeks of life is used to make the diagnosis of cCMV [15]. Early CMV testing of saliva or urine, ideally before 2–3 weeks of life, is important because a positive result after this timepoint is inconclusive for a congenital versus a postnatal CMV infection, and postnatal CMV infections are not associated with SNHL [16]. Saliva and urine PCR tests have been shown to be highly concordant with viral culture (97.5% and 96.3%, respectively). PCR testing has many advantages over viral culture, including lower cost, rapid turnaround, ability to be automated, and less variance with storage and transport conditions [17]. Dried saliva PCR testing has similar sensitivity and specificity to wet saliva testing, and samples are easier to store and transport [16, 18]. Although saliva samples are more easily collected than urine samples, there is a risk of false positive tests shortly after infants breastfeed, since CMV can be present in the breastmilk of seropositive mothers, and should undergo confirmatory testing from a urine specimen [19]. Urine samples can be collected from sterile urine bags or by placing cotton balls in infant diapers. Whereas cotton ball collection greatly reduces the sensitivity of viral culture when compared with samples collected from sterile urine bags, PCR testing was equivalent with the two collection methods [20].

Beyond the Neonatal Period

After the 3-week neonatal period, differentiating between congenital and postnatal CMV infection is no longer reliable using urine or saliva sampling. Viral shedding peaks at 1–2 years of age and declines steeply at age 5; a negative test result may be helpful for ruling out CMV infection as a possible diagnosis [21]. Testing dried blood spots (DBSs), which are routinely collected at birth in the USA and other countries for metabolic screening, have been proposed as an alternative method to detect cCMV infection. In the USA, the retention of DBS samples varies widely state to state from 1 month to indefinitely; for a majority of states (55%), they are kept for ≤ 5 years [22]. Though initial retrospective studies suggested high sensitivity and specificity for detecting cCMV infection using DBS samples [23–25], the National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) study published a large, population-based, prospective study that demonstrated significant limitations to this approach. In over 20,448 infants, two DBS PCR protocols were compared with the standard CMV culture assay. For the single-primer assay, the sensitivity was 28.3% (95% confidence interval [CI] 17.4–41.4%), and the two-primer assay was 34.4% (95% CI 18.6–53.2%). For both PCR methods, the specificity was 99.9% (95% CI 99.9–100%) [18]. In another study, they cite a low sensitivity of 42.3% (95% CI 23.4–63.1%) and a specificity of 73.3% (95% CI 67.6–78.5%) for DBS PCR [26•]. The low sensitivity of the DBS PCR method may be explained by technical factors associated with DNA extraction and PCR. This has limited the utility of DBS PCR testing as a CMV screening method. Instead, it has been used for the retrospective diagnosis of cCMV infection during the workup of SNHL of unknown etiology in infants older than 3 weeks of age. Because of the high specificity and low sensitivity, a positive result confirms a diagnosis of cCMV infection, but a negative result does not rule it out. CMV DBS testing is also a poor screening tool for identifying cCMV-associated SNHL; findings from the CHIMES study showed that CMV DBS failed to identify

greater than half of children who would develop SNHL [26•]. A summary of these diagnostic test interpretations is provided in Table 1.

Diagnostic Imaging

There are no specific cochlear or vestibular abnormalities seen on magnetic resonance imaging (MRI) or computed tomography (CT) in children with cCMV infections. However, there are characteristic neuroimaging findings associated with cCMV infection, and in children with these findings together with SNHL of unknown etiology, then cCMV infection should be strongly considered. Conversely, all children with SNHL found subsequently to have had cCMV infection should undergo brain imaging, either by MRI or ultrasound, to evaluate for these features, regardless of the presence of other symptoms associated with cCMV. These imaging findings include intracranial calcifications, ventriculomegaly, sulcation and gyration brain malformation, corpus callosum hypoplasia, cerebral and cerebellar volume loss, and white matter disease. Imaging scoring systems and profiles have been correlated to neurodevelopmental outcomes and used to identify candidates for antiviral treatment [27, 28].

Medical Management

Unlike other causes of hearing loss, which typically have no role for medical management, cCMV-associated SNHL is unique since antiviral medications—ganciclovir and valganciclovir—are available to treat the underlying CMV infection. Antiviral treatment is currently only indicated for symptomatic newborns with focal organ dysfunction or central nervous system involvement [29]. Traditionally, children with cCMV infection with only isolated hearing loss are considered asymptomatic [9]. There are three ongoing clinical trials (ClinicalTrials.gov identifiers NCT03301415, NCT03107871, and NCT01649869) evaluating the use of oral valganciclovir in asymptomatic cCMV-infected children in preventing the development or progression of SNHL in newborns < 1 month of age, between 1 and 5 months, and between 1 month and 4 years, respectively [30–32]. Research out of the Collaborative Antiviral Study Group (CASG) has evaluated the safety and effectiveness of antiviral treatments in newborns affected by cCMV. However, these studies have limited sample sizes and limited long-term hearing outcomes [27]. Their first trial included 100 newborns less than 1 month of age with confirmed symptomatic cCMV infection with central nervous system (CNS) involvement. Newborns were randomized to a 6-week course of intravenous (IV) ganciclovir or a placebo. No deterioration in hearing was found in the treatment group at 12 months based on auditory evoked brainstem responses (ABR), compared with 41% of controls. Unfortunately, patients in the treatment group were at greater risk of developing grade 3 or 4 neutropenia (63% in the treatment group versus 21% in the control group) [33].

The CASG established in a pharmacokinetic study of valganciclovir, an oral pro-drug of ganciclovir, that oral valganciclovir was able to achieve similar plasma concentrations of ganciclovir similar to intravenous ganciclovir. In addition to alleviating some of the challenge associated with long-term intravenous medication administration, valganciclovir was also found to have lower rates of developing neutropenia—38% percent of subjects, compared with 63% of those receiving IV ganciclovir [34]. In a 2015 CASG randomized control study, 96 infants were randomized to receiving 6 months or 6 weeks of oral valganciclovir treatment. Hearing at 6, 12, and 24 months, as well as neurodevelopmental outcomes, was measured. No difference was seen between the groups at 6 months, but at 12 and

Table 1 Interpretation of CMV testing modalities including urine and saliva (PCR and culture) and DBS PCR testing

Hearing status	CMV testing		Diagnosis
	Rapid culture or PCR of saliva and/or urine	DBS	
Normal	Negative at < 3 weeks	N/A	Normal hearing child, no cCMV
SNHL	Negative at < 3 weeks	N/A	Other cause for HL
Normal	Positive at < 3 weeks	N/A	Asymptomatic cCMV
SNHL	Positive at < 3 weeks	N/A	Symptomatic cCMV
Normal	Positive at > 3 weeks	Negative	Possible postnatal CMV, unable to rule out cCMV infection
SNHL	Positive at > 3 weeks	Negative	Possible postnatal CMV, unable to rule out cCMV infection as cause for HL
Normal	N/A	Positive	cCMV without current HL, monitor for progression
SNHL	N/A	Positive	Hearing loss likely due to cCMV

24 months, the 6-month treatment group exhibited higher odds of improvement or maintenance of total-ear hearing, as well as better neurodevelopmental scores compared with the 6-week group. Risk of grade 3 or 4 neutropenia in those receiving oral valganciclovir was 19% [35]. Finally, a small ($n = 16$) cohort study of children with symptomatic cCMV who were treated with valganciclovir and followed with auditory testing for an average of 3.2 years demonstrated measurable, but not statistically significant, worsening outcome in the best hearing ear, suggesting that improvements in hearing outcomes with valganciclovir treatment may be temporary. However, in this study with a small sample size, the length of valganciclovir treatment was variable: 6 children received less than 6 weeks, 7 children between 6 weeks and less than 6 months, and 3 children received 6 months of treatment [36]. Further study is required to determine the safety and long-term side effects of these antiviral medications, as well as the long-term effects on hearing and development, in order to establish whether they can be used in cCMV-infected children with isolated SNHL.

Newborn CMV Screening

There are two strategies for screening newborns for cCMV infection: a targeted method—where children who refer on their newborn hearing screening (NBHS) are tested for CMV infection—and universal screening for all newborns. In the USA, targeted newborn CMV screening has been implemented in five states: Connecticut, Illinois, Iowa, New York, and Utah [37]. In 2008, a targeted CMV screening program was implemented, in which children who did not pass their NBHS or had confirmed hearing loss underwent urine CMV culture. They found that 6% of children who failed their NBHS were infected with CMV, and 75% were identified on the basis of an abnormal hearing screening alone [38]. The same incidence of 6% CMV positivity in infants who failed NBHS was also seen in an Australian population [39].

Many children, as high as 90%, with cCMV infection will have no clinically apparent symptoms. It is estimated that 10–20% of these asymptomatic infants will develop SNHL [29, 40]. In a recent study, a NBHS-targeted CMV screening program was able to identify a majority of infants with CMV-related SNHL at birth. However, 43% of infants who would later be diagnosed with CMV-related hearing loss were not detected on NBHS [41••]. There is good evidence that universal CMV screening of all newborns is feasible [42, 43] and could significantly improve the clinical outcomes of those with delayed hearing loss. It is estimated that every year several thousands of children could benefit from early detection and interventions [44]. While targeted and universal screening methods have both been shown to be cost effective [45–47], universal screening provides the greatest opportunity to provide early, directed care and was shown to have a larger net savings despite higher associated testing costs [46].

Audiologic Evaluation and Rehabilitation

Audiologic Surveillance

Because cCMV-related hearing loss can have postnatal onset and frequently exhibits progression and fluctuation, it is important to closely monitor hearing throughout early childhood in all children with cCMV infection [8, 48]. However, few evidence-based guidelines exist regarding the frequency and duration of monitoring, and consensus has not been established. In a systematic review, 50% of delayed-onset hearing loss is identified in the first 14 months, 75% within 24 months, and none after 61 months (5.1 years); the mean age of onset was 18 months [29]. Most guidelines suggest a duration of follow-up through age 6, and one set of guidelines suggests follow-up through adolescence (age 19). The follow-up intervals are usually between 6 and 12 months, with the closest follow-up in the first 2–4 years after birth. A two-track strategy has been proposed in which newborns who refer on NBHS are retested at 2–6 weeks and then followed every 3 months until stability, and those who pass their NBHS get tested at 5 months then annually thereafter [5]. A summary of several proposed monitoring strategies is listed in Table 2.

Hearing Rehabilitation and Cochlear Implantation

Hearing rehabilitation for cCMV-related hearing loss is similar to congenital hearing loss of any other etiology. The goal is to maximize speech and language outcomes with early, regular hearing aid use and speech therapy when needed [27]. In children with severe-to-profound cCMV-related hearing loss, cochlear implantation can be performed. In cochlear implant (CI) recipients with cCMV infection, speech and language development show an overall improvement [51–53], and their outcomes are comparable with the general CI population [54] as well as children with GJB2-associated hearing loss [55, 56]. Given the risk of progressive hearing loss in children with cCMV, early cochlear implantation in cases of very asymmetric SNHL or single-sided deafness may be considered [57]. A recent study of CI outcomes in children with CMV-related hearing loss found a greater improvement in pure-tone hearing after cochlear implantation than with hearing aids, as well as word recognition and speech discrimination scores. Poor long-term outcomes were seen in children with motor or cognitive delays and brain abnormalities, and suggested that cCMV-associated developmental delays were important predictors of CI outcomes [58•]. MRI has been proposed as a method for stratifying the outcomes of CI recipients with cCMV infections [56], but a recent study found no correlation

Table 2 Screening strategy recommendations for cCMV-related hearing loss

Study/governing body	Surveillance recommendations
Fowler 1997 [48]	Every 6 months for 4 years, then can be made annual if there is no change, until 6–7 years of age
Dahle 2000 [49]	Every 6–12 months during the first 6 years of life
Goderis 2014 [29]	Annual follow-up until age 2 and, if normal at that time, to consider every-other-year testing through age 6
Foulon 2015 [5]	(A) If hearing loss is present on initial screen with ABR and OAEs, repeat ABR at 2–6 weeks. Then repeat testing (either ABR or behavioral audiometry) every 3 months until hearing is stable, then annually to age 6. (B) If hearing loss is not present on initial screen, follow-up OAE testing at 5 months, then at 1, 2, 3, 4, and 5 years. (C) If, at any time, the patient with previously normal hearing begins to show signs of hearing loss, switch to track A.
Kadambari 2011 [50]	National Deaf Children's Society (United Kingdom) guidelines recommend hearing assessment for infants with cCMV should be performed every 3–6 months in the first year until age 3 and then yearly until 6 years old.
Rawlinson 2017 [15]	Every 6 months for the first 3 years of life, and annually thereafter through adolescence (ages 10–19).

between severity of MRI findings and CI outcomes. Among 23 children with cCMV infection and severe-to-profound hearing SNHL, MRI findings were categorized into three groups (mild, moderate, and severe) and there was no association between MRI severity grade and hearing performance or speech development [59•].

Conclusion

Congenital CMV infection is the most common non-genetic cause of early-childhood SNHL. CMV testing is an important part of the workup of childhood SNHL. Incorporating CMV testing into newborn screening programs allows for improved clinical outcomes through early identification, directed care, and intervention. Currently, hearing-targeted screening is performed in parts of the USA and other countries, but NBHS can fail to detect infants with cCMV infections who later develop SNHL, and therefore, universal newborn CMV screening may be beneficial. Since cCMV-associated SNHL can have a late onset, progression, and fluctuation, close audiologic surveillance is required. Currently interventions available include antiviral drugs (ganciclovir and valganciclovir) for symptomatic cCMV-infected children, as well as hearing aids, speech therapy, and cochlear implants. A multi-disciplinary team consisting of otolaryngologists, audiologists, speech therapists, developmental pediatricians, and infectious disease specialists is required to assess and manage children affected by cCMV infections.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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