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American Cochlear Implant Alliance Position Statement on Newborn Congenital Cytomegalovirus Screening

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Abstract

It is estimated that 1 in every 200 US newborns has congenital cytomegalovirus (cCMV). Delayed identification of cCMV in newborns precludes timely intervention to mitigate sequelae of the infection such as hearing loss and other neurological complications. Newborn testing for cCMV enables appropriate diagnosis and intervention by multidisciplinary teams to properly manage the immediate sequelae of cCMV, avoid unnecessary additional testing that can result from delayed diagnosis, and monitor for future complications. It is the position of the American Cochlear Implant Alliance, the National CMV Foundation, and the American Academy of Otolaryngology–Head and Neck Surgery that universal newborn cCMV screening is necessary to best accomplish these goals.

Keywords

congenital cytomegalovirus, hearing loss, newborn screening

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Congenital cytomegalovirus (cCMV) occurs in roughly 1 in 200 live-born infants in the United States,[1] and up to 1 in 70 live births in low- and middle-income countries.[2] In the United States, cCMV represents a health disparities issue, with disproportionately higher rates found among lower-income and marginalized racial/ethnic groups.[3] Furthermore, cCMV is a leading cause of permanent disability in children causing a range of conditions including sensorineural hearing loss (SNHL), intellectual disability, vision loss, and cerebral palsy.[4,5] Of those born with cCMV, 10% to 15% will have clinically apparent or *symptomatic* disease at birth, over half of whom will develop long-term disabilities from the infection.[6] The remaining 85% to 90% of infants are born with clinically inapparent, or *asymptomatic* infections. These infants appear typical at birth however up to 20% will develop SNHL in childhood[7]; emerging research points to nearly half developing gaze, balance and vestibular disorders.[8,9] All of these children are at risk of a significant, costly diagnostic odyssey to determine the etiology of their seemingly disparate symptoms and clinical findings in the absence of newborn testing. As federal and state legislators begin to consider the utility of universal newborn screening, the American Cochlear Implant Alliance initiated, together with the American Academy of Otolaryngology–Head and Neck Surgery and the National CMV (Cytomegalovirus) Foundation, a multidisciplinary task force to form a position statement on universal newborn cCMV screening based on available evidence.

Hearing Outcomes in cCMV

Congenital CMV is thought to account for up to 13% to 20% of all childhood-onset SNHL.[10-13] Infants with

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symptomatic cCMV disease are at the highest risk for hearing loss, occurring at rates at or above 40%.[6,14,15] Goderis et al collapsed quantitative findings from 10 studies in a systematic review and reported hearing loss in 32.8% of symptomatic cases with individual studies reporting rates exceeding 40%.[16] Infants with asymptomatic infections appear to be at reduced risk for many of the neurodevelopmental sequelae that accompany symptomatic infection,[17] although they remain at significant risk for late-onset and progressive SNHL.[18] Prospective data from the CHIMES multicenter study identified hearing loss in 2.9% and 11.3% of asymptomatic infants at 6- and 12-month intervals, respectively, showing a rapid window for deterioration of hearing.[1] In the Goderis study, authors also found hearing loss in 9.9% of asymptomatic infants after at least 2 hearing evaluations over several years in childhood.[16] In a cohort followed until 18 years of age, Lanzieri et al found SNHL in 25% of those with asymptomatic cCMV.[7]

Congenital CMV-associated SNHL can be challenging to detect because there are variable presentations: it can be present at birth, late onset and/or progressive in nature.[19] The decline in hearing status in those with cCMV can be rapid. One study found that only 57% of infants with cCMV who will develop hearing loss in the neonatal period will refer on their newborn hearing screen.[1] Changes in hearing status have been reported as late as 18 years of age.[7] Hearing loss has been reported as flat, and while the degree of loss can vary, a large proportion falls in the severe to profound range.[19] Children with cCMV are more likely to present with unilateral, progressive, and profound hearing losses compared to a non-cCMV hearing loss control group.[19] Progressive and late-onset SNHL are common in children with either symptomatic or asymptomatic cCMV.[18,20,21]

Screening for cCMV

Rationale For cCMV Screening in the Newborn Period

As most infants with cCMV are born without clinical signs, screening programs are needed to identify these infants early. A number of reports have noted that cCMV infection is routinely underdiagnosed in routine practice.[18,22-24] Diagnosis of cCMV must be performed using a specimen collected in the neonatal period (before 21 days of age), otherwise it is challenging to distinguish an acquired post-natal CMV infection (not associated with SNHL or developmental delays), from a congenital infection.[25,26] Furthermore, guidelines recommend early antiviral treatment for those who qualify. For treatment to be effective it must be initiated early in infancy.[25,26]

Current State of cCMV Screening

There is a paucity of data related to the frequency of cCMV screening or testing in the US. What is known is that Minnesota became the first state to implement a universal cCMV screening program based on neonatal dried blood spot (DBS) testing in 2023.[27] New York and Connecticut are set to follow-suit in the near future. To date, 13 states have hearing targeted screening legislative or public health mandates (Colorado, Connecticut, Florida, Illinois, Iowa, Kentucky, Louisiana, Maine, New York, Pennsylvania, Texas, Virginia, and Utah).[28] Beyond state-mandated screening programs, many hospitals and health systems have implemented cCMV screening programs. A cross-sectional survey of pediatric infectious disease practices across the United States found that 65% reported a protocol for neonatal CMV screening or testing.[29]

Screening Approaches

There are 3 main approaches to neonatal screening for cCMV. Hearing targeted cCMV testing utilizes universal newborn hearing screening programs. Since the most common sequela of cCMV infection is hearing loss, this strategy attempts to identify those most at risk for CMV-mediated hearing loss.[30] Most programs will test the newborn following a failed or referred hearing screen at the birth hospital or after the first outpatient hearing screening appointment. An expanded targeted testing approach seeks to identify not just those with failed newborn hearing screening but also those with subtle isolated signs or symptoms consistent with a cCMV infection (eg, small for gestational age). Suarez et al reported a greater than 3-fold increase in cCMV-diagnosed infants over hearing-targeted testing and a prevalence rate of symptomatic cases comparable to those expected for universal cCMV screening.[31] Current universal cCMV programs rely on polymerase chain reaction (PCR) testing of neonatal dried blood samples that are routinely obtained for all newborns for metabolic and genetic screening. These programs screen all infants and do not restrict testing to only those with certain clinical findings. The rates of cCMV positivity for hearing targeted and universal cCMV testing were recently reported from a prospective survey of 82 birth hospitals at 1.5% and 0.5%, respectively.[32] Outside of the first 3 weeks of life, cCMV can only be diagnosed using a retrospective sample collected during that time, such as the DBS.[33] As such, it is critical that the remaining DBS sample be stored by the state newborn screening program for years after the child's birth for future testing should clinical suspicion arise. Furthermore, at present, DBS CMV PCR has a lower sensitivity (roughly 80%),[27] meaning that up to 20% of cases will be missed using DBS-based universal screening. However, while DBS testing may be somewhat insensitive for the detection of infection compared to other methods, it does appear in 1 study to be accurate in detecting newborns with congenital CMV infection who will develop hearing loss.[33] Future retesting for cCMV using more sensitive assays, when developed, will only be possible if DBS samples are retained.

Treatment and Intervention

Comprehensive Care Approach

Early detection of cCMV benefits children with both congenital and late-onset hearing loss through improved access to interdisciplinary assessment and management. Hearing loss is only 1 symptom among a host of sequelae that may be subtle at birth and/or underdiagnosed in the absence of confirmatory testing for cCMV.[18,22-24] Children with cCMV should receive referrals to related professionals to complete a baseline assessment soon after identification and characterize the extent of the disease.[25] An infectious disease specialist is likely to be a key member of this care team in the newborn period, and may recommend antiviral medication in certain cases. A randomized controlled trial of infants with symptomatic cCMV found that a 6-month (vs 6 weeks) course of valganciclovir modestly improved developmental outcomes 2 years after treatment.[34] Some studies have found evidence that antiviral treatment has a protective effect on hearing thresholds to prevent further progression of hearing loss.[35,36] The long-term durability of hearing benefits is less clear.[37]

Additional members of the child's optimal clinical team ideally should include otolaryngology, audiology, ophthalmology, and speech-language pathology.[38] Children also may require other specialists such as a developmental pediatrician, neurologist, and physical therapist as warranted on an individual basis to meet each child's and family's needs as both initial and ongoing providers.[38]

Audiological Monitoring

Only universal screening will improve the early detection of and intervention for all cCMV-positive infants who experience late-onset hearing loss. Late identification of hearing loss is associated with a host of adverse consequences on language development and educational attainment.[39,40] When late-onset or progressive hearing loss is ultimately detected, it may be only after a protracted period of parental concern. Children with hearing loss may also receive months or years of intervention with insufficient auditory access to benefit from these efforts.

The risk of late-onset hearing loss and progressive hearing loss in cCMV-infected infants requires increased surveillance of hearing sensitivity in the childhood years.[38] Dahle and et al found that the delay in the onset of hearing loss occurred over a range from 6 months to 16.4 years.[41] Given this finding, a minimum surveillance schedule should include serial evaluations with a pediatric audiologist through 6 years of age and continued audiologic follow-up through the teenage years.[38,42] Comprehensive hearing evaluation in this age group should include measures of hearing sensitivity using frequency-specific stimuli (objective and/or behavioral as the child is able), otoacoustic emissions, tympanometry using an appropriate probe frequency, case history, and parent-report observations of responses to auditory stimulation. In addition to prospective monitoring visits, managing teams should encourage parents to report new hearing concerns without delay. Children with cCMV are at high risk of balance, stability and coordination disorders due to vestibular dysfunction, which may be progressive or late onset in nature.[9,43] Vestibular function should be evaluated and monitored as part of otolaryngology/audiology follow-up.[43]

Technology and Intervention

Infants and children with SNHL secondary to cCMV may be candidates for hearing aids or cochlear implants based on their degree of hearing loss and the family's preference for a certain communication modality. Even slight/mild degrees of hearing loss may compromise auditory access to important speech and language cues. Clinical practice guidelines in pediatric audiology recommend the full-time use of well-fit hearing technology for children who are candidates, whether for unilateral or bilateral hearing loss.[44] Hearing aids provide auditory access by amplifying the incoming signal to sensation levels where the child can detect and use auditory information for learning.[45] Cochlear implants restore auditory access by delivering sounds directly to the auditory nerve and are a better choice when children do not have sufficient residual hearing to benefit from hearing aids (typically hearing loss at the moderately severe or poorer range). As children with cCMV-related hearing loss may initially present with unilateral hearing loss and may progress to bilateral loss over time,[46] candidacy for hearing technology must be considered on an ear-specific basis (including unilateral cochlear implantation). Success with technology will vary, especially in those with neurodevelopmental sequelae; the range of additional disabilities may impact outcomes.[14,47-49] Children who are otherwise asymptomatic with no sequelae other than SNHL have been found to have CI outcomes similar to other children receiving CI.[50] Given that children with cCMV are also at risk for additional delays and disorders, such as those impacting communication, the need for immediate, high-quality intervention is especially urgent, as is diligent monitoring of developmental milestones. In addition to the provision of appropriate, well-fit hearing technology, parents of children with cCMV-related hearing loss should foster a language-rich environment to develop communication skills.

Challenges and Considerations

Predicting the onset, progression and final severity of SNHL in infants with cCMV remains a significant challenge, especially in asymptomatic infants.[51,52] This makes early identification of all infants with cCMV through universal screening critically important, however convenient testing platforms (eg, high throughput PCR) using DBS are limited by their lower sensitivity, which may result in up to a 20% to 30% false negative rate as compared to point-of-care saliva or urine testing.[27,53,54]

Long-term developmental outcomes in children with cCMV vary widely,[17] with emerging research showing increased risk of vestibular dysfunction, coordination difficulties and autism spectrum disorder.[55] Even with timely hearing rehabilitation with hearing aids or cochlear implants, some children with cCMV and SNHL may be unable to utilize listening and spoken language as their primary means of communication, although other significant benefits of hearing may be present.[14,46-49] More research is needed to identify prognostic factors, and best practices regarding supporting communication in children with cCMV, which may include early introduction of multimodal communication. Parents and caregivers of children who are CI candidates should be counseled accordingly regarding possible outcomes.

Conclusion

Emerging evidence substantiates the need for universal newborn screening for cCMV. The American Cochlear Implant Alliance initiated, together with the American Academy of Otolaryngology–Head and Neck Surgery and the National CMV Foundation, a multidisciplinary task force to form a position statement on universal newborn screening based on available evidence.

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Author Contributions

Megan Honor Pesch, contributed to the conceptualization, outlining, drafting, and finalization of the manuscript, incorporated all feedback into the final draft of the manuscript and was responsible for submission to the journal, signed off on the final submission; **Kevin David Brown**, contributed to the conceptualization, outlining, drafting and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission; **Amy L. Birath**, contributed to the conceptualization, outlining, drafting and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission; **Gail J. Demmler-Harrison**, contributed to the conceptualization, outlining, drafting and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission; **Caitlin Sapp**, contributed to the conceptualization, outlining, drafting, and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission; **Anne Morgan Selleck**, contributed to the conceptualization, outlining, drafting, and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission; **Alex D. Sweeney**, contributed to the conceptualization, outlining, drafting, and finalization of the manuscript, provided critical feedback on the final version of the manuscript and signed off on the final submission. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures

Competing interests: Megan Honor Pesch serves on the board of directors of the National CMV Foundation, is a consultant for MedScape/Web MD, Diasorin, and Moderna. Alex D. Sweeney has had recent consultancy agreements with Cochlear Americas, MED-EL GmbH, Advanced Bionics, and Oticon Medical.

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