Congenital Cytomegalovirus Infection: Audiologic Outcome

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The association between congenital cytomegalovirus (CMV) infection and sensorineural hearing loss (SNHL) was first described almost 50 years ago. Studies over the intervening decades have further described the relationship between congenital CMV infection and SNHL in children. However, congenital CMV infection remains a leading cause of SNHL in children in the United States and the world today. As more CMV infections are identified, it is important to recognize that infants who are born to seroimmune mothers are not completely protected from SNHL, although their hearing loss is often milder than that seen in CMV-infected infants following primary maternal infections. Late-onset and progressive hearing losses occur following congenital CMV infection, and CMV-infected infants should be evaluated regularly to provide for early detection of hearing loss and appropriate intervention. Fluctuating hearing loss that is not explained by concurrent middle ear infections is another characteristic of CMV-related hearing loss in children. Challenges still remain in predicting which children with congenital CMV infection will develop hearing loss and, among those who do develop loss, whether or not the loss will continue to deteriorate.

Keywords. cytomegalovirus; congenital infection; sensorineural hearing loss.

Congenital cytomegalovirus (CMV) infection continues to be a public health problem because of its frequency and its role in sensorineural hearing loss (SNHL) in infants and young children. Outcome following congenital CMV infection is highly variable, ranging from no apparent sequelae to multiple sensory impairments [1–3]. Approximately 40%–60% of symptomatic infants with congenital CMV infection have permanent sequelae. In addition, even infants without clinically apparent CMV infection (asymptomatic) are not protected from permanent sequelae as 10%–15% of asymptomatic infants will have some type of permanent impairment. Although infants with congenital CMV infection may have cognitive impairment, retinitis, and/or cerebral palsy following infection, by far SNHL is the most common sequelae following congenital CMV infection.

Studies have estimated that approximately half of symptomatic infants will have SNHL following infection, and that about 10%–15% of the asymptomatic infants will also develop SNHL [1–4]. These percentages equate to approximately 800–1200 infants with symptomatic congenital CMV infection and an additional 1800–2700 infants with asymptomatic congenital CMV infection who will have CMV-related SNHL each year in the United States. These numbers show that congenital CMV infection is the leading nongenetic cause of SNHL in children in the United States. In fact, Morton and Nance estimated that 21% of all hearing loss at birth is due to congenital CMV infection and that by 4 years of age 25% of childhood hearing loss is due to congenital CMV infection [5].

CMV-RELATED HEARING LOSS MAY OCCUR WHETHER THE MOTHER HAS A PRIMARY INFECTION OR IS SEROIMMUNE PRIOR TO PREGNANCY

CMV-related hearing loss may occur whether the mother acquires the virus for the first time during pregnancy (primary infection) or is seroimmune (presence

of CMV immunoglobulin G) prior to pregnancy. Fowler et al in 1992 reported that of the infants who were born with congenital CMV infection and whose mothers had a primary infection during pregnancy, 15% developed SNHL, and of those approximately 50% of them had severe bilateral hearing loss [6]. Similarly, Foulon et al in 2008 found that 15% of CMV-infected infants of mothers with primary infections had SNHL, and half of these had bilateral hearing loss [7]. However, although based on very low numbers, Yamamoto et al in 2011 reported in their predominantly CMV-seropositive population that 33% of the CMV-positive infants following maternal primary infections had SNHL and all of their hearing loss was bilateral in nature [8].

Infants who are born to seroimmune mothers are not completely protected from SNHL, although the severity of their hearing loss may be milder than that which is seen in CMV-infected infants following primary maternal infections. Ross et al in 2006 found that 11% of CMV-infected infants whose mothers were seroimmune before pregnancy had SNHL, with approximately 25% of them having severe bilateral hearing loss [9]. Similarly, Yamamoto et al reported that 15% of the CMV-infected infants whose mothers were seroimmune before pregnancy had SNHL, with approximately one-third of those having bilateral hearing loss [8]. These data suggest that infected infants born to mothers with preexisting immunity are contributing significantly to CMV-related SNHL, although with less severity of loss. This is an important global consideration as most of Asia, South America, and Africa have populations with high CMV seropositivity, so it is likely that the majority of CMV-infected infants in these regions will be born to mothers with previous exposures to CMV.

LATE-ONSET AND PROGRESSIVE HEARING LOSSES OCCUR FOLLOWING CONGENITAL CMV INFECTION

Hearing loss following congenital CMV infection may be present at birth or occur later in the first years of life. Approximately 33% to 50% of SNHL due to congenital CMV infection is late-onset loss [2]. Late-onset hearing loss occurs throughout the first several years of life with the median age for late-onset hearing loss occurring 11 months later (at 44 months of age) in asymptomatic children than in symptomatic children, indicating that children with congenital CMV infection should be evaluated for hearing function at least annually until 5–6 years of age [10]. Approximately 50% of children with SNHL following congenital CMV infection will continue to have further deterioration or progression of their loss [10, 11]. The rate of hearing loss progression in congenital CMV infection seems to be similar regardless of whether the child had an asymptomatic or a symptomatic infection, although the symptomatic infants

have a greater degree of severity and also earlier progression of their hearing loss [10]. Another characteristic of CMV-related hearing loss is fluctuating hearing loss that is not explained by concurrent middle ear infections. Fluctuating hearing loss may occur in only one ear or at only a few frequencies within the ear or occur in both ears if a child has bilateral hearing loss. About 50% of children with hearing loss following an asymptomatic congenital CMV infection will have fluctuating hearing loss, whereas only about 30% of children with hearing loss following a symptomatic CMV infection will have fluctuating loss [10]. Besides the type of infection at birth (symptomatic or asymptomatic), no other data exist to predict which child with hearing loss will also have a fluctuating pattern of loss. Additionally, the challenge of obtaining repeated hearing evaluations at times when a young child does not have concurrent middle ear infections has made it difficult to identify patterns, if any, in fluctuating losses.

The ongoing CMV and Hearing Multicenter Screening (CHIMES) study funded by the National Institute on Deafness and Other Communication Disorders (NIDCD) is currently evaluating the long-term audiologic outcome in children with congenital CMV infection at 7 sites in the United States. Preliminary data indicate that infants with CMV infection are more likely to refer or not pass their newborn hearing screening than infants who do not have CMV infection [12]. These data suggest that newborn hearing screening is effectively identifying most of CMV-related hearing loss that is present at birth. However, early data from the CHIMES study also suggest that some infants are being missed by newborn hearing screening either due to the presence of milder hearing impairments or the fact that the hearing loss is occurring after the newborn period [12]. These data are consistent with previous published studies. The final summary from the CHIMES study will be forthcoming in the next few years when long-term follow-up of CMV-infected infants is complete.

CHILDREN WITH CONGENITAL CMV INFECTION WILL NEED MORE FREQUENT MONITORING OF THEIR HEARING STATUS DURING THE EARLY YEARS OF LIFE

Because SNHL is the most common sequela following congenital CMV infection and late-onset and progressive losses may occur, infants with CMV infection should be evaluated regularly to provide for early detection of suspected hearing loss and appropriate intervention [13]. Frequent audiologic monitoring at 6-month intervals until age 5 years should be strongly considered, with the possibility of more frequent monitoring every 3 months when hearing levels are changing or until the child is talking. For symptomatic infants with cognitive impairments, cerebral palsy, or vision loss, adjustments in audiologic

assessments might be needed. Challenges to frequent monitoring of hearing status in children with congenital CMV infection include frequent ear infections in young children, resulting in a conductive overlay for SNHL and a delay in obtaining baseline audiologic data, and the difficulty of securing parental compliance in scheduling repeated assessments. Due to the fluctuating and progressive nature of some of the CMV-related hearing losses, special attention should be focused on children with hearing aids to maintain proper amplification during times when hearing levels are changing.

In conclusion, challenges to understanding and preventing CMV-related SNHL remain. Because CMV infection can only be reliably diagnosed in the first weeks of life, the identification of infants with asymptomatic congenital CMV infection will not happen unless CMV testing takes place in the newborn period. Without CMV screening, the burden of CMV-related hearing loss in children with asymptomatic congenital CMV infection is not known. Virologic or immunologic markers that may indicate which children with congenital CMV infection will develop CMV-related hearing loss remain undefined. Also, predicting late-onset or progressive hearing losses in children with congenital CMV infection continues to be a challenge. In addition, questions about treatment for reducing or ameliorating hearing loss due to CMV remain. Does treatment with antivirals at birth prevent late-onset and progressive losses that could occur after treatment ends? For those infants who have fluctuating hearing loss, how will treatment success be measured? Continued research is needed to provide further understanding of CMV-related hearing loss and to develop future interventions that could reduce or eliminate SNHL due to congenital CMV infection.

Notes

References

1. Pass RF, Fowler KB, Boppana S. Clinical importance of cytomegalovirus infection: an overview. In: Excerpta Medica International Congress Series, Progress in Cytomegalovirus Research 1991:3–10.
2. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss due to congenital cytomegalovirus infection be missed? J Pediatr 1999; 135:60–4.
3. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007; 17:355–63.
4. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. J Clin Virol 2006; 35:226–31.
5. Morton CC, Nance WE. Newborn hearing screening—a silent revolution. N Engl J Med 2006; 354:2151–64.
6. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992; 326:663–67.
7. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. J Pediatr 2008; 153:84–8.
8. Yamamoto AY, Mussi-Pinhata MM, Isaac M de L, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. Pediatr Infect Dis J 2011; 30:1043–6.
9. Ross SA, Fowler KB, Ashrith G, et al. Hearing loss in children with congenital CMV infection born to mothers with preexisting immunity. J Pediatr 2006; 148:332–6.
10. Dahle AJ, Fowler KB, Wright JR, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol 2000; 11:283–90.
11. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr 1997; 130:624–30.
12. Fowler KB, Tolan RW, Ahmed A, et al. Interim findings of the importance of congenital cytomegalovirus infection in the etiology of childhood hearing loss. In: Abstract Proceedings of the 13th International CMV/BetaHerpesvirus Workshop, Nuremberg, Germany, 14–17 May 2011.
13. Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 2007; 120:898–921.