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Review

Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: A quantitative assessment☆

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Abstract

Background: Congenital cytomegalovirus (CMV) infection is a cause of sensorineural hearing loss (SNHL) in children, but the magnitude of its contribution is uncertain. Quantifying the impact of congenital CMV infection requires an evidence-based assessment using a standard case definition of hearing loss.
Objectives: To determine the frequency of bilateral moderate to profound SNHL in children with congenital CMV infection and to estimate the CMV-attributable fraction of bilateral moderate to profound SNHL.
Study design: A systematic review of studies of children with congenital CMV infection ascertained in an unbiased manner through universal newborn screening for CMV using viral culture in urine or saliva specimens in combination with a review of the literature on congenital CMV infection and hearing loss, including articles of all types.
Results: Approximately, 14% of children with congenital CMV infection develop SNHL of some type, and 3–5% develop bilateral moderate to profound SNHL. Among all children with bilateral moderate to profound SNHL, we estimate that 15–20% of cases are attributable to congenital CMV infection.
Conclusions: Congenital CMV infection is one of the most important causes of hearing loss in young children, second only to genetic mutations, and is potentially preventable.
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Keywords: Sensorineural; Late-onset; Newborn screening; Developmental disability; Sequelae

Contents

Abbreviations: CMV, cytomegalovirus; dB, decibels; PBHL, permanent bilateral hearing loss; SNHL, sensorineural hearing loss; UAB, University of Alabama at Birmingham.

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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1. Introduction

Congenital infection with cytomegalovirus (CMV) is an important, often underappreciated cause of permanent bilateral hearing loss (PBHL) (Barbi et al., 2003; Fowler and Boppana, 2006; Pass, 2005). Human CMV is a member of the herpesvirus family that is spread through close interpersonal contact with infected bodily fluids, notably urine, saliva, blood, and genital secretions. Congenital CMV infection occurs as a result of either a primary or recurrent infection acquired during pregnancy. Individual studies from industrialized countries typically report a congenital CMV birth prevalence of 0.3–1.2% (Pass, 2005). Two systematic reviews report that on average, 0.7% of children are infected with CMV at birth (Dollard et al., 2007; Kenneson and Cannon, 2007), although reliable, national-level estimates are not available and this may be an underestimate. CMV is the most common potentially disabling perinatal infectious disease.

Hearing loss is a common sequela of congenital CMV infection, occurring in 10–15% of infected children (Dahle et al., 2000; Dollard et al., 2007; D.S. Ross et al., 2006; S.A. Ross et al., 2006). Hearing loss reportedly occurs in 30–40% of children symptomatic at birth with cytomegalovirus inclusion disease (CID) and in 5–10% of children with asymptomatic infections. Hearing loss from congenital CMV infection can be either unilateral or bilateral and varies from mild to profound in terms of degree. Reportedly, approximately half of hearing losses due to congenital CMV infection are late-onset or progressive and, therefore, cannot be detected at birth through newborn hearing screening (Fowler et al., 1999).

This paper reviews the evidence on the contribution of congenital CMV infection to moderate to profound PBHL in children. The percentage of PBHL in children attributed to congenital CMV infection is often reported to be approximately 30% (Barbi et al., 2003; Fowler and Boppana, 2006; Fowler and Pass, 1995). However, inconsistent case definitions of hearing loss in CMV studies make it difficult to draw firm conclusions. Our purpose is to estimate the number of cases of moderate to profound bilateral hearing loss associated with congenital CMV infections, the type of hearing loss for which cost estimates are available (Centers for Disease Control and Prevention, 2004). The findings from this review will be used in a subsequent study to estimate the potential economic impacts of interventions to prevent or ameliorate the effects of congenital CMV infection. Ours is the first study since Fowler and Pass (1995) that compares estimates of the frequency of PBHL due to CMV in combination with published estimates of the overall number of children with permanent bilateral moderate to profound hearing loss.

2. Methods

This review draws upon a recent systematic review of the literature on the neurological and sensory sequelae of congenital CMV infections, which was limited to studies that performed universal screening of all infants born at a given center or centers using either urine or saliva specimens to culture for CMV (Dollard et al., 2007). Such studies are assumed to be representative of the populations the centers serve. Studies that used immunoglobulin M assays of blood specimens to screen for congenital CMV infection were excluded because the assays lack sensitivity, and infants identified with congenital CMV by such assays are unlikely to be representative. To avoid overrepresentation of infants with sequelae, Dollard and colleagues excluded studies in which any children with CMV infection were referred based on clinical symptoms and those based on screening subsets of infants at elevated risk for congenital CMV infection. The systematic review by Dollard et al. (2007) identified 11 studies that conducted audiological follow-up. This paper includes those 11 studies as well as published studies with audiological follow-up of cohorts of children with congenital CMV infection that were enriched with children referred on the basis of a clinical CMV diagnosis or risk factors. The case definition of hearing loss is one of the most important methodological issues for an economic analysis of the cost of hearing loss. Hearing loss can be bilateral or unilateral. Studies of CMV infection and hearing loss have typically included both unilateral and bilateral hearing losses. In contrast, most epidemiologic studies of hearing loss are restricted to PBHL, which comprises three types of hearing losses: conductive, sensorineural, and mixed. Conductive hearing loss originates from impairment in the middle ear that prevents sounds from being efficiently transferred through the outer ear canal to the eardrum via the tiny bones, or ossicles. Although some types of conductive losses can be permanent, most are caused by fluid in the middle ear resulting from infections that either resolve on their own or can be treated with antibiotics. Other kinds of conductive losses, such as those caused by congenital structural abnormalities of the middle ear, can usually be corrected with surgery. Sensorineural hearing loss (SNHL) results from damage in the inner ear (cochlea) or in the auditory nerve and is permanent. A "mixed" loss means there is both a conductive and sensorineural component to the hearing loss. Because congenital CMV infection is associated with SNHL only, studies of congenital CMV and hearing loss have typically restricted "hearing loss" to SNHL. Although CMV has been found in the middle ear effusions of children with otitis media with effusion (Chonmaitree et al., 1992) the present study does not address the role of postnatal CMV infection in hearing loss.

The other critical aspect of the case definition for PBHL is the threshold of hearing loss in the better ear. A 40 dB threshold of hearing loss in the better ear is commonly used to define bilateral hearing loss in children in population-based surveillance (Barbi et al., 2003; Bhasin et al., 2006; Drews et al., 1994; Fortnum and Davis, 1997). The same definition has been used in studies of the economic costs associated with hearing loss (Centers for Disease Control and Prevention, 2004; Schroeder et al., 2006). To facilitate

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comparison between the prevalence of hearing loss caused by congenital CMV infection and the published literature on the prevalence of hearing loss in general, the definition of hearing loss used for this article includes all permanent sensorineural hearing losses that are bilateral and 40 dB or greater. Our exclusion of unilateral and mild bilateral hearing loss is not intended to diminish the importance of continued study of these types of hearing losses, including their impact on school performance.

3. Results

3.1. Probability of SNHL

Dollard et al. (2007) identified 11 prospective studies that reported SNHL among 67 of 606 (11%) children with asymptomatic infections and 25 of 72 (35%) children with symptomatic infections. With an average of 12.7% classified as having symptomatic infections, the weighted average of SNHL was 14.1%. Fowler and Boppana (2006) identified eight prospective studies that reported rates of SNHL in 75 of 863 (8.7%) children with asymptomatic infections and 100 of 241 (41%) with symptomatic infections. Seven studies were common to the two reviews. Dollard et al. excluded one study (Dahle et al., 2000) based on a sample enriched for children with sequelae but included a different study from the same institution based on a sample identified through universal screening (Fowler et al., 1999). Dollard et al. also included three small cohort studies, with a total of 34 children, all asymptomatic at birth.

The most complete data on hearing loss among children with congenital CMV infection comes from studies conducted at the University of Alabama at Birmingham (UAB). Fowler et al. (1999) reported that there were 388 children with congenital CMV infection identified through newborn screening at the UAB hospital in 1980–1996 and followed with repeated audiologic assessment. Among these children, 57 (15%) were identified with SNHL at a threshold of 20 dB at 72 months of age, including 38 of 335 (11%) asymptomatic children and 19 of 53 (36%) children who were symptomatic at birth (Fowler et al., 1999). Length of follow-up is important, because only 59% of children diagnosed with SNHL at 72 months had been identified by 12 months of age (Fowler et al., 1999).

Other analyses reported on a group of 860 children born in Birmingham during 1966–1999 who were identified with congenital CMV infection and received long-term follow-up (Dahle et al., 2000; Fowler and Boppana, 2006). Only 63% of those children were born at the UAB hospital and detected by newborn screening; the remaining 37% were born elsewhere and referred to UAB after developing symptoms or sequelae of congenital CMV infection (Fowler and Boppana, 2006). The overall percentage of children with SNHL at a threshold of 20 dB diagnosed up to the age of 15 years was 15%, including 48 of 651 (7.4%) asymptomatic children and 85 of 209 (41%) children with symptomatic infection. Among 437 children with CMV who were born at UAB hospital during 1985–2002 and had audiologic follow-up, 14% were identified with SNHL (Fowler and Boppana, 2006). These findings are similar to those reported by Fowler et al. (1999) for 1980–1996 births screened at UAB.

The distribution of SNHL cases in congenital CMV infection by laterality and threshold of hearing loss is unclear (Table 1). Among UAB studies, Hicks et al. (1993) reported that only 21% of children with SNHL had a hearing loss below 50 dB and none below 30 dB. In contrast, Fowler et al. (1999) reported that 44% of all SNHL cases had a hearing loss below 30 dB. Hicks et al. (1993) reported that 9 of 14 (64%) cases of SNHL were bilateral. Similarly, Dahle et al. (2000) reported that 80 of 143 (56%) cases of SNHL were bilateral; Fowler et al. (1999) did not report data on laterality. In contrast, S.A. Ross et al. (2006) reported that only 11 of 32 (34%) children had bilateral SNHL. Other studies have reported varying percentages of bilateral hearing loss among children with SNHL associated with congenital CMV infection: 25% (Kumar et al., 1984), 60% (Barbi et al., 2003), 76% (Madden et al., 2005), and 80–90% (Ahlfors et al., 1999; Ogawa et al., 2007).

One direct estimate of the frequency of moderate to profound PBHL among an unbiased sample of children with congenital CMV infection detected through routine screening has been reported at 5% (Hicks et al., 1993). If the 8.3% prevalence of SNHL at a threshold of 30 dB among children with congenital CMV infection reported by Fowler et al. (1999) is combined with the 60% frequency of bilateral

Table 1
Laterality of hearing loss in children with congenital CMV infection

Study	Location	Threshold of hearing loss (dB)	Unilateral SNHL, *N*	Bilateral SNHL, *N*	Percent bilateral
Kumar et al. (1984)	Ohio	20	3	1	25
Ahlfors et al. (1999)	Sweden	NR	1	4	80
Hicks et al. (1993)	Alabama	30	5	9	64
Dahle et al. (2000)	Alabama	20	63	80	56
Barbi et al. (2003)	Italy	40	43	65	60
S.A. Ross et al. (2006)	Alabama	20	21	11	34
Ogawa et al. (2007)	Japan	20	4	63	94

NR: not reported.

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Table 2
Prevalence of congenital CMV infection among children with bilateral SNHL

Study	Location	Number with bilateral SNHL/all SNHL	Number with congenital CMV	Prevalence
Barbi et al. (2003)	Italy	65/130	13/22	20%/17%
Ogawa et al. (2007)	Japan	55/67	9/10	16%/15%

hearing loss reported by Dahle et al. (2000), the prevalence of moderate to profound PBHL among children with congenital CMV infection would be 5%, the same as reported by Hicks.

Estimation of the number of cases of PBHL attributed to congenital CMV infection requires the birth prevalence of congenital CMV infection. Two systematic reviews by Kenneson and Cannon (2007) and Dollard et al. (2007) reported average birth prevalence estimates of 0.65% and 0.7%, respectively. Assuming a birth prevalence of 0.7% and a risk of bilateral moderate to profound SNHL of 3–5%, the projected risk of moderate to profound PBHL due to congenital CMV infection is 0.21–0.35 per 1000 births.

3.2. Attributable fraction of bilateral SNHL

When congenital CMV infection is not systematically assessed in children by laboratory screening of specimens taken soon after birth, it is greatly underreported as a cause of SNHL, with fewer than 4% of cases attributed to congenital CMV (Dent et al., 2004; Fowler and Boppana, 2006; Morzaria et al., 2004). For example, Madden et al. (2005) reported that 1.4% of children identified with SNHL had a symptomatic congenital CMV infection. One retrospective etiologic study of hearing loss by Ohlms et al. (1999) reported that among 114 children with hearing loss evaluated during 1985–1995 at a hospital in Houston, TX, 21 (18%) had a diagnosis of congenital CMV infection. It was not stated whether the children were screened for CMV at birth or what method of screening was used. Only 100 of the children were classified as having SNHL; the remaining children either had conductive or mixed losses, with no indication of laterality.

At least two studies have used systematic newborn assessments among children with diagnosed SNHL to directly determine the fraction of cases of hearing loss attributable to congenital CMV infection (Table 2). First, Barbi et al. (2003) reported congenital CMV infection in 22 of 130 (17%) children with SNHL greater than 40 dB. This included 9 of 87 (10%) children with hearing loss detected soon after birth and 13 of 43 (30%) children with hearing loss of unknown cause who were diagnosed more than 3 months after birth. Among 65 children with bilateral SNHL, 13 (20%) had congenital CMV infection. All 13 children had severe to profound SNHL, accounting for 27% of the 48 children in that category.

The most direct and up-to-date estimate of the attributable fraction of SNHL due to CMV comes from a recent study from Japan. Ogawa et al. (2007) analyzed stored dried umbilical cord samples for 67 children diagnosed with SNHL, 10 (15%) of whom were found to have congenital CMV infection on the basis of detection of viral DNA. Among 55 children who had moderately severe to profound bilateral SNHL (>55 dB), 9 (16%) had congenital CMV infection. Among the subset of 36 children with profound bilateral SNHL (>90 dB), 8 (22%) had congenital CMV infection.

Other studies have taken an indirect approach by combining estimates of SNHL among children with congenital CMV infections with other estimates of prevalence of SNHL in children. For example, Harris et al. (1984) reported that 4 out of 43 (9.3%) children with congenital CMV infection identified through newborn screening and with audiologic follow-up testing in Sweden had bilateral deafness. The authors projected that 10 children would have bilateral deafness based on other Swedish data, implying a 40% attributable fraction. However, a subsequent publication from the same cohort study reported 4 out of 76 (5.3%) children with congenital CMV infection to have bilateral deafness, with one additional child having unilateral deafness (Ahlfors et al., 1999). The final results from the Swedish cohort reported by Ahlfors et al. (1999) imply a 23% attributable fraction.

Similarly, Peckham et al. (1987) combined an estimate of 0.3% birth prevalence of congenital CMV infection from a UK study by Peckham et al. (1983), a 6% (1/17) US estimate of bilateral SNHL among children with congenital CMV infection from Kumar et al. (1984), and a UK estimate of 1.5 per 1000 children with bilateral SNHL to calculate a 12% attributable fraction. However, the one case of SNHL in the US study cited (Kumar et al., 1984) did not meet the threshold for moderate hearing loss used in the UK prevalence estimates. In the United States, 1.5 per 1000 children are diagnosed with bilateral hearing loss of 40 dB or greater (CDC, 2004). For a birth prevalence of 0.7%, and a frequency of bilateral SNHL among those with congenital CMV infection of 3–5%, the attributable fraction is in the range of 14–23%.

4. Discussion

As many as 5% of children with congenital CMV infection develop moderate to profound bilateral hearing loss by 6 years of age, and up to 15% of children develop any type of SNHL. An estimate of the average birth prevalence of congenital CMV infection derived from universal screening studies conducted in industrialized countries is 0.7% (Dollard et al., 2007; Kenneson and Cannon, 2007). Based on that birth prevalence, it is estimated that perhaps 3.5 per 10,000 children born each year in high-income countries develop moderate to profound bilateral SNHL as a result of congenital CMV infection.

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Congenital CMV infection is an important cause of PBHL, but the exact magnitude is uncertain. Published reports suggest that congenital CMV accounts for 25–40% of PBHL in children (Barbi et al., 2006; Fowler and Pass, 1995; Morton and Nance, 2006; Ornoy and Diav-Citrin, 2006). Morton and Nance (2006) cited Barbi et al. (2003) as the basis for their estimate that congenital CMV accounts for 25% of "deafness" in children at 4 years of age. Our estimate, based on a review of empirical studies, is that 15–20% of cases of moderate to profound PBHL are associated with congenital CMV infection. Barbi et al. (2003) reported evidence of congenital CMV in 17% of all children with hearing loss and 20% of those with bilateral hearing loss. Among children with profound PBHL, congenital CMV infection is reportedly associated with 22–27% of cases (Ahlfors et al., 1999; Barbi et al., 2003; Harris et al., 1984; Ogawa et al., 2007).

One reason for the discrepancy between our estimate of 15–20% for the attributable fraction of PBHL due to congenital CMV and previous estimates of 25–40% is lack of consistent definitions of hearing loss. If only profound PBHL is considered, 25% is a reasonable estimate and Morton and Nance (2006) specifically referred to deafness. The frequently cited 40% attributable fraction estimate (e.g., Fowler and Pass, 1995) originated from a 1984 report by Harris et al. on the basis of preliminary data from a Swedish study of children with "bilateral deafness." The subsequent full report of the study reported a much lower rate of bilateral profound hearing loss consistent with an attributable fraction of 23% (Ahlfors et al., 1999). Another explanation is confusion over the findings of a study by Italian investigators. Barbi et al. (2003) reported that perhaps one-third of cases of PBHL without a known cause could be attributed to congenital CMV infection. However, because half or more of PBHL cases in children have a known cause, that estimate would be misleading if applied to all PBHL.

The pathogenesis of hearing loss caused by congenital CMV infection is still being elucidated. Autopsy studies of infants with severe congenital CMV infection have provided evidence that SNHL is associated with changes in temporal bone structure which results from viral infection of the inner ear (Schleiss and Choo, 2006). Furthermore, studies where CMV quantitative PCR was used for measuring CMV in the blood of newborns showed that higher viral loads correlated with a higher likelihood of hearing loss. If CMV viral load were to be validated as a predictive marker of risk for development of SNHL, this assay could be used for prognostic purposes and for making decisions about antiviral therapy and other interventions. Newborn screening for congenital CMV could be an important complement to newborn hearing screening in the early detection and management of hearing loss. Primary prevention of congenital CMV through hygiene education and, ultimately, development of a new vaccine, should be considered as part of a strategy for the prevention of serious hearing loss in children (D.S. Ross et al., 2006; S.A. Ross et al., 2006; Schleiss and Choo, 2006).

This paper has not addressed the many cases of SNHL in children with congenital CMV infection that are mild, unilateral, or both. Unilateral and mild bilateral hearing losses are the subjects of research to assess long-term implications, which is beyond the scope of this paper (Bess et al., 1998; Workshop Proceedings, 2005). It would be useful to identify the fraction of cases of all degrees and laterality of hearing losses that are caused by congenital CMV infection. However, until there is comprehensive population surveillance for mild and unilateral hearing loss in children, it will be difficult to conduct such a study.

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