Hearing Trajectory in Children with Congenital Cytomegalovirus Infection

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Abstract

Objectives. To compare hearing trajectories among children with symptomatic and asymptomatic congenital cytomegalovirus infection through age 18 years and to identify brain abnormalities associated with sensorineural hearing loss (SNHL) in asymptomatic case patients.

Study Design. Longitudinal prospective cohort study.

Setting. Tertiary medical center.

Subjects and Methods. The study included 96 case patients (4 symptomatic and 92 asymptomatic) identified through hospital-based newborn cytomegalovirus screening from 1982 to 1992 and 72 symptomatic case patients identified through referrals from 1993 to 2005. We used growth curve modeling to analyze hearing thresholds (0.5-8 kHz) by ear with increasing age and Cox regression to determine abnormal findings on head computed tomography scan associated with SNHL (hearing threshold >25 dB in any audiometric frequency) among asymptomatic case patients.

Results. Fifty-six (74%) symptomatic and 20 (22%) asymptomatic case patients had SNHL: congenital/early-onset SNHL was diagnosed in 78 (51%) and 10 (5%) ears, respectively, and delayed-onset SNHL in 25 (17%) and 20 (11%) ears; 49 (32%) and 154 (84%) ears had normal hearing. In affected ears, all frequency-specific hearing thresholds worsened with age. Congenital/early-onset SNHL was significantly worse (severe-profound range, 70 dB) than delayed-onset SNHL (mild-moderate range, 26-55 db). Frequency-specific hearing thresholds were significantly different between symptomatic and asymptomatic case patients at 0.5 to 1 kHz but not at higher frequencies (2-8 kHz). Among asymptomatic case patients, white matter lucency in asymptomatic case patients was significantly associated with SNHL by age 5 years.

Conclusion. Congenital/early-onset SNHL frequently resulted in severe to profound loss in symptomatic and asymptomatic case patients. White matter lucency in asymptomatic case patients was significantly associated with SNHL by age 5 years.

Keywords

congenital cytomegalovirus infection, sensorineural hearing loss

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In the United States, an estimated 15% to 20% of all cases of bilateral moderate to profound sensorineural hearing loss (SNHL) among young children are attributable to congenital cytomegalovirus (CMV) infection. Among an estimated 20,000 (0.5%) US children born with congenital CMV infection annually, approximately 10% may present with symptomatic disease at birth. Moderately to severely symptomatic disease manifests with central nervous system involvement (microcephaly, chorioretinitis, SNHL, or brain abnormalities) or multiple signs attributable to congenital CMV infection, such as thrombocytopenia, petechiae, hepatosplenomegaly, hepatitis, and intrauterine growth restriction. Mildly symptomatic disease may occur with 1 or 2 signs that are mild and transient (eg, mild hepatomegaly).

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Currently, congenital CMV infection with no apparent abnormalities except SNHL is defined as asymptomatic congenital CMV infection with isolated SNHL. The proportion of infants diagnosed with SNHL within 8 weeks of life is much higher among those with symptomatic disease at birth as compared with asymptomatic ones (38% vs 5%). However, infants with asymptomatic infection may account for a greater number of SNHL cases. Moreover, an estimated 5% of children with asymptomatic congenital CMV infection—about 900 children annually in the United States—have severe hearing loss in at least 1 ear by age 12 months. Half of these children meet current candidacy criteria for cochlear implantation by age 5 years.

Microcephaly and abnormal head computed tomography (CT) scan findings indicative of tissue destruction and dysplastic growth have been associated with an increased risk of SNHL among infants with symptomatic congenital CMV disease at birth. Among infants with asymptomatic congenital CMV infection, periventricular radiolucency as well as intracranial calcifications in head CT scans have been associated with increased risk of SNHL. Although these findings suggest that it may be possible to identify children with asymptomatic congenital CMV infection at risk for SNHL in whom monitoring should be considered, additional studies with larger sample sizes and longer audiologic follow-up are needed to assess the relationship between brain imaging abnormalities and SNHL in asymptomatic congenital CMV infection.

Delayed-onset, progressive, and fluctuating SNHL in children with congenital CMV infection has been described in several studies. In the largest follow-up study describing SNHL and hearing threshold variability in children with congenital CMV infection, the median age at the last audiological evaluation of all children was 5 years. In the present study, we compared hearing trajectories among children with symptomatic and asymptomatic congenital CMV infection identified with SNHL from infancy through age 18 years and assessed brain abnormalities associated with SNHL among children with asymptomatic congenital CMV infection.

**Methods**

Our study included infants with congenital CMV infection enrolled in the Congenital Cytomegalovirus Longitudinal Study, identified by routine CMV screening of all newborns at Women’s Hospital of Texas (Houston, Texas) from 1982 to 1992 or through referrals from 1983 to 2005. Congenital CMV infection was diagnosed by culture of urine collected within 3 days (routine screening) to 3 weeks of life (referrals).

We classified congenitally infected infants as symptomatic or asymptomatic case patients based on the presence or absence, respectively, of at least 1 of the following CMV-related signs at birth: purpura/petechia, jaundice, hepatosplenomegaly, microcephaly, unexplained neurologic abnormality, elevated liver enzymes (alanine aminotransferase >100 IU), hyperbilirubinemia (total bilirubin >3 mg/dL), hemolytic anemia, or thrombocytopenia (platelet count <75,000/mm³). Infants who were small for gestational age or had congenital SNHL in the absence of at least 1 of the aforementioned signs were classified as asymptomatic case patients. The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals approved the study protocol.

Case patients had neuroimaging evaluations performed by unenhanced head CT scans by 8 months of age and received hearing evaluations (tympanometry, auditory brainstem response [ABR], and behavioral audiometry) annually up to age 6 years and at least once during elementary, middle, and high school years. Per study protocol, during the neonatal period, case patients were screened with broadband click ABR (2-4 kHz) at 35 dB. At age 0 to 2 years (or older for case patients with cognitive impairment), ABR was performed under conscious sedation with either broadband click or frequency-specific tone burst stimuli (0.5-8 kHz). At age ≥3 years, behavioral audiometry was performed with pure tone air and bone conduction testing (0.25-8 kHz). Currently, Texas Children’s Hospital adheres to a 2-step newborn hearing screening protocol with otoacoustic emissions and, for those who fail, automated ABR.

For this analysis, we combined ABR with pure tone air conduction thresholds as follows: (1) ABR response threshold elicited by broadband click stimuli with pure tone thresholds at 2 and 4 kHz and (2) frequency-specific ABR response threshold elicited by tone burst stimuli with pure tone thresholds, after subtraction of 10 dB for 0.5, 1, and 8 kHz and 0 dB for 2 and 4 kHz from the tone burst thresholds. We excluded assessments in which tympanometry suggested presence of conductive hearing loss. For any audiometric frequency with “no response” recorded at the maximum output of the hearing testing equipment, we estimated the hearing threshold by adding 5 dB to the maximum output of the equipment. We defined SNHL as ≥25-dB hearing threshold for the broadband click ABR or at any frequency for the corrected tone burst or pure tone air conduction results. We categorized SNHL for each ear as (1) congenital/early onset when detected by the first ABR assessment at age ≤12 months and confirmed in subsequent assessments or (2) delayed-onset when detected after ≥1 assessments with normal hearing, as previously described. We categorized frequency-specific hearing thresholds as normal when ≤15 dB and the severity of hearing loss as follows: slight (16-25 dB), mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90 dB), and profound (≥90 dB). To compare hearing trajectories (ie, hearing thresholds at each audiometric frequency from 0.5 to 8 kHz for each ear with increasing age) among symptomatic and asymptomatic case patients, we used growth curve modeling. This is a multilevel regression technique used for longitudinal data to simultaneously analyze group- and individual-level effects. As an exploratory step, we first plotted the observed data with smoothers (ie, splines), overlaying the individual profiles with the average trend lines at each hearing level. We subsequently
plotted the corresponding fixed effects models from ordinary least squares regression (ie, the predicted mean stratified by hearing status and status at birth). We fit models that included the child’s age, status at birth (ie, symptomatic vs asymptomatic), hearing status (congenital/early-onset SNHL, delayed-onset SNHL, or normal hearing), and an interaction term for age and hearing status. We did not adjust for multiple comparisons, because the number of variables included in the models was small. We used SAS’s MIXED procedure, incorporating random effects for intercepts (starting hearing thresholds) and slopes (rate of change in hearing thresholds) and a variance component covariance structure.

To assess whether selected abnormal head CT findings of tissue destruction (ie, intracranial calcification, white matter lucency) within 8 months of birth were associated with SNHL among asymptomatic case patients, we used the Cox proportional hazards regression model and the Firth method to reduce small sample size bias.16 We calculated hazard ratios and 95% CIs and considered results with a P value < .05 as statistically significant. For all analyses, we used SAS 9.3 (SAS Institute Inc, Cary, North Carolina).

**Results**

Our study included 168 infants with congenital CMV infection: 96 (57%) case patients identified through routine CMV screening from 1982 to 1992, including 4 (4%) symptomatic and 92 asymptomatic case patients and 72 symptomatic case patients identified through referrals, among whom 51 (71%) were born before and 21 (29%) after the Texas Newborn Hearing Screening Program was established in 1999.

Among 76 symptomatic case patients, 44 (58%) had congenital/early-onset SNHL: 26 (59%) had evaluations by ABR and behavioral audiometry and 18 (41%) only by ABR. Among 92 asymptomatic case patients, 9 (10%) had congenital/early-onset SNHL, all of whom had evaluations by ABR and behavioral audiometry. Of 83 asymptomatic case patients without congenital/early-onset SNHL, 8 (10%) were not further evaluated by ABR. **Table 1** shows the median ages at the first and last ABR and behavioral audiometry for symptomatic and asymptomatic case patients, with or without congenital/early-onset SNHL.

At the end of follow-up, 56 (74%) symptomatic case patients and 20 (22%) asymptomatic case patients had SNHL (**Figure 1**), among whom 47 (84%) and 10 (50%) had bilateral SNHL, respectively. The majority (72%) of the 47 symptomatic case patients with bilateral loss had congenital/early-onset bilateral loss as compared with 10% of the asymptomatic case patients (P < .001).

Our analysis with growth curve modeling to assess hearing trajectories included symptomatic and asymptomatic case patients, among whom 78 (51%) and 10 (5%) ears were diagnosed with congenital/early-onset SNHL, respectively, 25 (17%) and 20 (11%) with delayed-onset SNHL, 49 (32%) and 154 (84%) ears with normal hearing. Frequency-specific hearing thresholds were significantly worse in ears with congenital/early-onset SNHL as compared with ears with congenital/early-onset SNHL as compared with ears with delayed-onset SNHL, especially after 2 to 3 years of age (**Figure 2**). We found significant differences in frequency-specific hearing thresholds between symptomatic and asymptomatic case patients only at 0.5 and 1 kHz but not at any of the higher frequencies (**Table 2**). SNHL severity worsened with age for symptomatic and asymptomatic case patients. Severity worsened for congenital/early-onset and delayed-onset SNHL and at all frequency-specific hearing thresholds (**Table 2**). Among symptomatic and asymptomatic case patients, ears with congenital/early-onset SNHL progressed to severe/profound

### Table 1. Hearing Evaluations by ABR or Behavioral Audiometry among Symptomatic and Asymptomatic Case Patients by Hearing Status.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Status at Birth: Congenital or Early-Onset SNHL</th>
<th>n</th>
<th>Age at First Evaluation, y</th>
<th>Age at Last Evaluation, y</th>
<th>Evaluations, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>44</td>
<td>0.05 (0.01-3)</td>
<td>2 (0.16-15)</td>
<td>6 (1-17)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>31</td>
<td>0.13 (0.01-1)</td>
<td>1 (0.01-18)</td>
<td>2 (1-16)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>9</td>
<td>0.2 (0.08-0.9)</td>
<td>2 (0.9-4)</td>
<td>4 (1-6)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>83</td>
<td>0.2 (0.01-1)</td>
<td>1 (0.01-4)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td><strong>Behavioral audiometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>26</td>
<td>4 (1-12)</td>
<td>12 (1-18)</td>
<td>5 (1-22)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>23</td>
<td>4 (1-10)</td>
<td>13 (3-18)</td>
<td>5 (1-16)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>9</td>
<td>5 (3-9)</td>
<td>17 (13-18)</td>
<td>8 (2-10)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>75</td>
<td>4 (1-17)</td>
<td>17 (3-18)</td>
<td>5 (1-13)</td>
</tr>
</tbody>
</table>

Abbreviations: ABR, auditory brainstem response; SNHL, sensorineural hearing loss.
loss in all frequencies. Ears with congenital/early-onset SNHL had mean frequency-specific hearing thresholds in the range of moderate to severe at birth, progressing to severe/profound loss by early childhood (Figure 2). Ears with delayed-onset SNHL had mean frequency-specific hearing thresholds in the range of moderate to moderately severe later in childhood (Figure 2). Overall, frequency-specific hearing thresholds deteriorated at a rate of 1 to 3 dB per year for ears with congenital/early-onset SNHL and 1 to 4 dB per year for ears with delayed-onset SNHL (Table 2).

Among 92 asymptomatic case patients, 87 (95%) had a head CT scan performed within the first 8 months of life. Eighteen (20%) asymptomatic case patients had abnormal findings categorized as tissue destruction: 11 (61%) had white matter lucency; 5 (28%) had intracranial calcifications; and 2 (11%) had malacia. Figure 3 presents head CT scans of asymptomatic case patients showing white matter lucency (periventricular leukomalacia) not associated with prematurity and periventricular punctate calcifications.

The proportion of asymptomatic case patients with congenital/early-onset SNHL was greater among those with brain abnormalities than those without, but the associations were not statistically significant (Table 3). By age 5 years, SNHL was diagnosed in 4 of 11 (36%) asymptomatic case patients with white matter lucency versus 6 of 67 (9%) without (hazard ratio, 4.4; 95% CI, 1.3-15.6; \( P < .05 \)). SNHL by age 18 years was also significantly associated with white matter lucency (Table 3).

**Discussion**

In this study based on longitudinal hearing assessments from infancy up to 18 years of age, congenital/early-onset SNHL frequently progressed to severe or profound hearing loss by 5 years of age, regardless of the presence of CMV-related signs at birth. A majority of the asymptomatic case patients with congenital/early-onset SNHL had unilateral loss at onset, but most of these children developed SNHL in the contralateral ear by age 18 years. The progression of delayed-onset SNHL was similar among asymptomatic and symptomatic case patients. Children with congenital/early-onset SNHL had worse hearing thresholds by 18 years of age on average when compared with children with delayed-onset SNHL.

Universal newborn screening for congenital CMV infection has the potential to identify children at risk for SNHL who could benefit from regular monitoring and earlier intervention.17 A better understanding of age of onset and risk factors for SNHL in children with asymptomatic congenital CMV infection could inform clinical guidance regarding frequency, duration, and type of audiologic monitoring that these children should receive. A recent study suggested that either universal or targeted newborn screening, a strategy of CMV testing of infants who failed the newborn hearing screening, appears to be cost-effective.15 However, no additional cost was assumed for public health infrastructure required for CMV screening with saliva specimens.19,20 Additionally, the study assumed that 1% of infants with asymptomatic congenital CMV infection would require further neuroimaging evaluation by magnetic resonance imaging (MRI).18 In contrast, 20% of the asymptomatic case patients in our cohort had brain imaging abnormalities. More data are needed to inform the evaluation of the potential costs and benefits of newborn screening for CMV.

We found that children with asymptomatic congenital CMV infection who had white matter lucency were roughly 4 times as likely to be diagnosed with SNHL by age 5 years as those without white matter lucency. In another study, white matter lucency was associated with a retrospective diagnosis of asymptomatic congenital CMV infection in children who later developed static encephalopathy.21 To avoid ionizing radiation from CT, cranial ultrasound and
MRI are currently the preferred methods for neuroimaging evaluation of infants with congenital CMV infection. Although cranial ultrasound is a relatively low-cost technique that is readily available in most centers, it does not reveal white matter abnormalities. MRI is recommended for investigation of cortical, white matter, and
Consensus guidance on using neuroimaging to evaluate infants with asymptomatic congenital CMV infection is needed. Furthermore, the definition of symptomatic congenital CMV disease is likely to evolve as prognostic markers of long-term impairments are elucidated and data from clinical trials of antiviral treatment of newborns with asymptomatic congenital CMV infection and isolated SNHL become available. Currently, antivirals are not recommended for routine use in this population.

The development and maturation of the auditory system occur in a stepwise fashion. The cochlea acquires an adult-like configuration by the end of the second trimester of pregnancy, but the myelination continues throughout the perinatal period and early and later childhood. Previous neuroimaging studies of infants with congenital CMV infection indicated that the pattern of brain abnormalities varies with timing of CMV infection during pregnancy. Loss of neurons and glia suggests CMV infection before 18 weeks of pregnancy. Migrational abnormalities, such as polymicrogyria, which have been observed in symptomatic but not asymptomatic case patients, suggest CMV infection during 18 to 24 weeks' gestation. Delayed myelination, dysmyelination, and white matter disease (as observed in our asymptomatic case patients) suggest CMV infection at 26 weeks of pregnancy. It is possible that CMV-related SNHL could occur as a consequence of fetal infection at any time during pregnancy. A better understanding of brain imaging findings associated with CMV-related SNHL could provide insights into SNHL pathogenesis and timing of CMV infection during pregnancy. Animal models have suggested that the potential mechanisms for CMV-related SNHL are host-derived inflammatory responses and not direct virus-mediated cytopathology. A better understanding of the mechanisms for CMV-related SNHL could inform development of therapeutic options to prevent onset and further progression of SNHL in children with congenital CMV infection.

Our study had limitations. Symptomatic case patients were identified through referrals and likely reflect relatively severe cases. The small number of asymptomatic case

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**Table 2.** Estimates from Growth Curve Modeling Predicting Frequency-Specific Hearing Thresholds.

<table>
<thead>
<tr>
<th>Audiometric Frequency, kHz</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
<td>Estimate</td>
<td>SD</td>
<td>Estimate</td>
<td>SD</td>
<td>Estimate</td>
</tr>
<tr>
<td>Intercept</td>
<td>8.1</td>
<td>1.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.3</td>
<td>1.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.4</td>
</tr>
<tr>
<td>Status at birth: symptomatic&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.6</td>
<td>2.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>14.6</td>
<td>3.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.7</td>
</tr>
<tr>
<td>Hearing status&lt;sup&gt;e&lt;/sup&gt;</td>
<td>59.4</td>
<td>3.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>85.0</td>
<td>3.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>63.9</td>
</tr>
<tr>
<td>Congenital/early-onset SNHL</td>
<td>15.7</td>
<td>4.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25.4</td>
<td>3.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.0</td>
</tr>
<tr>
<td>Age</td>
<td>0.0</td>
<td>0.1</td>
<td>0.0</td>
<td>0.1</td>
<td>-0.6</td>
</tr>
<tr>
<td>Interaction: age and hearing status&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.0</td>
<td>0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6</td>
<td>0.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.0</td>
</tr>
<tr>
<td>Age × congenital/early-onset SNHL</td>
<td>2.4</td>
<td>0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5</td>
<td>0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.3</td>
</tr>
<tr>
<td>Age × delayed-onset SNHL</td>
<td>2.0</td>
<td>0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.6</td>
<td>0.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Abbreviation: SNHL, sensorineural hearing loss.

<sup>a</sup>The estimate indicates the difference in hearing level (dB) that would be associated with specific factors as compared with the reference group, controlling for the other variables in the model. For example, the hearing level at 0.5 kHz was 6.6 dB higher (worse) among symptomatic versus asymptomatic case patients, after controlling for hearing status, age, and the interaction between age and hearing status. P value <.05 considered statistically significant; model results based on SAS Proc Mixed.

<sup>b</sup>P <.0001.

<sup>c</sup>P <.05.

<sup>d</sup>Reference: asymptomatic.

<sup>e</sup>Reference: normal hearing.

<sup>f</sup>Reference: age normal hearing.

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**Figure 3.** Head computed tomography scans from children with asymptomatic congenital cytomegalovirus infection: (A) white matter lucency (periventricular leukomalacia) not associated with prematurity; (B) periventricular punctate calcification.
Table 3. Cox Proportional Hazards Regression Analysis: Head Computed Tomography Scan and Sensorineural Hearing Loss among Children with Asymptomatic Congenital CMV Infection.

<table>
<thead>
<tr>
<th>Brain Abnormality</th>
<th>Congenital/Early-Onset SNHL</th>
<th>SNHL by Age 5 y</th>
<th>SNHL by Age 18 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Intracranial calcifications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter lucency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue destruction</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; HR, hazard ratio; SNHL, sensorineural hearing loss.

*The data reflect the number and proportion of asymptomatic case patients with or without brain abnormalities diagnosed with or without SNHL.

Patients with congenital/early-onset SNHL limited the statistical power to find significant associations with brain abnormalities and congenital/early-onset SNHL. Different audiologic equipment were used over the years, and the variation in maximum intensity output at each frequency over the course of the study could have resulted in underestimates of hearing thresholds for some frequencies. Data were not available for all audiometric frequencies at all ages, because testing of many symptomatic case patients with developmental delays or cognitive impairment relied on ABR. Frequency-specific tone burst ABR was not available for all audiometric frequencies at all ages, because testing of many symptomatic case patients with developmental delays or cognitive impairment relied on ABR. Frequency-specific tone burst ABR was not available for all case patients at younger ages, which could have resulted in missed SNHL.

In this study, we used growth curve modeling to analyze longitudinal data on hearing thresholds. Growth curve modeling includes fixed and random effects to describe the general trajectory for the group as a whole and for the individuals within the group. We compared ears with congenital/early-onset SNHL among symptomatic and asymptomatic case patients and found no differences in hearing thresholds at higher frequencies (2, 4, and 8 kHz). The observed means of the hearing thresholds suggested a steeper progression of SNHL during early childhood, although the predicted means increased linearly with age. The statistically significant difference in the predicted means of hearing thresholds at the lower frequencies needs further clarification. Many symptomatic case patients evaluated only by ABR missed data for 0.5 and 1 kHz. The differences of 7 to 15 dB among symptomatic relative to asymptomatic case patients at 0.5 and 1 kHz may not be clinically relevant when we consider that hearing thresholds in ears with congenital/early-onset SNHL differed from normal hearing ears by 60 to 85 dB.

Previously, we reported that 5% of our asymptomatic case patients identified through newborn screening had SNHL >70 dB HL in at least 1 ear by age 12 months. This figure corresponds to 900 children annually in the United States, half of whom would meet current candidacy criteria for cochlear implantation by age 5 years. The CMV and Hearing Multicenter Screening Study, which screened >100,000 newborns for CMV in the United States, found a 7-fold rate of failure in newborn hearing screening among congenitally infected versus uninfected infants. Nonetheless, in the absence of universal screening for congenital CMV infection, nearly half the infants with asymptomatic congenital CMV infection who present with SNHL within 8 weeks of life would be missed by newborn hearing screening. Targeted CMV screening of newborns who fail the newborn hearing screening will still miss a large portion of infants with congenital CMV infection, either symptomatic or asymptomatic at birth, who are at risk of developing SNHL early in life.

In our cohort, infants with asymptomatic congenital CMV infection who were diagnosed with SNHL during the first 2 years of life had lower full-scale intelligence and receptive vocabulary scores as compared with uninfected children. Although the Joint Committee on Infant Hearing in 2007 endorsed audiologic monitoring of children identified with congenital CMV infection, a consensus is needed including how often, for how long, or by whom testing should be performed. Infants with congenital CMV infection, regardless of the presence of other signs at birth, who pass newborn hearing screening often develop SNHL, which can progress to severe or profound levels in early childhood. Therefore, early detection of CMV-related SNHL during infancy is important to allow for timely intervention to optimize language development.

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**Author Contributions**

Tatiana M. Lanzieri, conceptualized and conducted analysis contained in this report, interpreted the data, led the writing of the initial manuscript and revised versions, and approved the final version; Winnie Chung, conceptualized the analysis contained in this report, reviewed and interpreted individual audiologic data, revised the manuscript and approved the final version; Jessica Leung, conducted analysis contained in this report, interpreted the data, revised the manuscript and approved the final version; A. Chantal Caviness, was the co–principal investigator for the Congenital Cytomegalovirus Longitudinal Study, revised individual clinical, laboratory and head computed tomography data, revised the manuscript and approved the final version; Jason L. Baumgardner, conducted analysis contained in this report, interpreted the data, revised the manuscript and approved the final version; Peggy Blum, conceptualized and provided audiologic follow-up in the Congenital Cytomegalovirus Longitudinal Study, revised the manuscript and approved the final version; Stephanie R. Bialek, conceptualized the analysis contained in this report, interpreted the data, revised the manuscript and approved the final version; Gail Demmler-Harrison, served as the principal investigator for the Congenital Cytomegalovirus Longitudinal Study, provided patient follow-up, conceptualized the analysis contained in this report, interpreted the data, revised the manuscript and approved the final version.

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**References**


