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Cytomegalovirus Shedding and Delayed Sensorineural Hearing Loss: Results from Longitudinal Follow-Up of Children with Congenital Infection

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Keywords

congenital cytomegalovirus; cytomegalovirus; sensorineural hearing loss; longitudinal studies

Cytomegalovirus (CMV) infection is common in the U.S.,[1] frequently occurring among pregnant women[2] whose babies are therefore at risk for congenital infection.[3] Congenital CMV infection is a leading cause of sensorineural hearing loss and is responsible for an estimated 15%–25% of all clinically significant hearing loss among U.S. children.[4,5] Among children with congenital CMV infection, hearing loss often presents at birth, but in many instances may develop only after months or even years.[6–8]

The pathogenesis of CMV-related hearing loss is not well-understood, although it has been hypothesized that both direct cytopathic effects and localized inflammatory responses may play a role.[9] CMV antigens can be found in the inner ear of human infants[10,11] and guinea pigs in experimental models.[12] A clinical trial reported that symptomatic newborns with central nervous system (CNS) involvement who were treated for 6-weeks with ganciclovir, an agent known to be active against CMV, were less likely to have new or progressive hearing loss, indirect evidence that CMV replication is important for the pathogenesis of hearing loss.[13] Additional human studies have shown that CMV shedding at birth, especially in large amounts (*e.g.*, >25,000 genomic equivalents per mL), is associated with an increased risk of hearing loss.[14–16] However, Noyola et al.[17] found that children with hearing loss and progressive hearing loss were less likely to shed CMV for extended periods of time, raising the possibility that host immune responses related to viral clearance may be associated with hearing loss.

A better understanding of the causes of delayed hearing loss is important for identifying high-risk children who need intensive audiologic follow-up and who may be candidates for anti-viral therapies or early interventions to improve speech, language, or cognitive development. To learn more about the pathogenesis of CMV-related hearing loss, we examined the relationship between persistent viral shedding and delayed hearing loss in a large number of children born with congenital CMV.

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The findings and conclusions in this article have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.

MATERIALS AND METHODS

Study population

We retrospectively identified children who were born between January 1980 and October 1997, had congenital CMV infection by virologic testing of urine obtained within the first 2 weeks of life, and had at least 1 hearing evaluation and a CMV culture result from at least 1 follow-up visit. These children had been enrolled in several different studies with varying duration of follow-up. 445 (77%) were identified at the University of Alabama at Birmingham (UAB) hospitals and 135 (23%) were identified through referral to UAB from other hospitals in the region. Of these 580 children, 160 (28%) were classified as having symptomatic congenital CMV infection because they were culture-positive for CMV and exhibited one or more of the following symptoms in the newborn period: petechiae, jaundice with conjugated hyperbilirubinemia (direct bilirubin >2 mg/dL), hepatosplenomegaly, microcephaly, seizures, or chorioretinitis. Because patient recruitment included referrals, the proportion of symptomatic infants in this study (28%) was much higher than the proportion (10%–15%) typically found in studies using population-based screening.[5] The 420 children with none of these symptoms at birth were classified as having asymptomatic congenital CMV infection. This retrospective data analysis was approved by the UAB human subjects review board, with the stipulation that Centers for Disease Control and Prevention (CDC) investigators not receive patient identifiers so that their participation in data analysis would not constitute human subjects research.

Hearing evaluations

The children were followed in a special interdisciplinary clinic at UAB and were monitored with serial audiologic evaluations using a standard protocol as described previously.[9] Depending on the child's age and developmental level, audiologic evaluations consisted of assessment with auditory brainstem response (ABR), emittance measures of middle ear function, and/or pure-tone and speech audiometry. Audiologic assessments using ABR were typically done between 3 and 8 weeks of age and again at 6 to 12 months of age. Behavioral audiometric evaluations using visual reinforcement procedures were performed beginning at 9 months of age, with follow-up assessments every 6 months until valid pure-tone thresholds via play audiometry could be obtained for each ear, which usually occurred between 2 ½ and 3 years of age. Thereafter, children were evaluated annually unless test results or parental concerns indicated a need for additional audiologic assessment.

Hearing loss was defined as air conduction thresholds >25 dB on ABR or >20 dB on behavioral audiometric evaluations in conjunction with normal bone conduction thresholds and normal middle ear function.[6,9] Children with conductive hearing impairment that resolved were not classified as having hearing loss. Delayed onset hearing loss was defined as one or more hearing evaluations with a normal threshold documented for each ear prior to the detection of hearing loss in one or both ears.

Specimen collection and virus isolation

At most study visits, urine and saliva samples were obtained from children, although at some visits one or both of these samples could not be obtained. Samples were collected, processed, and stored as described elsewhere.[18]

Routine cell culture isolation of CMV involved the inoculation of locally prepared human foreskin fibroblasts with either a urine or saliva sample aliquot followed by careful observation of the culture for the characteristic cytopathic effects (CPE) produced by CMV. Cultures were examined once or twice a week for a minimum of 5 weeks for the appearance of CPE due to CMV.[18] A child was considered to be shedding at a particular visit if he or she had a positive

culture result in either urine or saliva. Viral culture results were not quantitative and we did not carry out CMV genotyping. We defined and evaluated persistent CMV shedding using both frequency of shedding (*e.g.*, number or percentage of positive cultures) and duration of shedding (*e.g.*, age at last positive culture), but excluded results from the initial diagnosis of congenital CMV since all were shedding at that visit. Intermittent shedding was defined as a negative culture at one visit and a positive culture at a subsequent visit.

Statistical Methods

Data were analyzed using SAS Version 9.00 (SAS Institute Inc., Cary, NC). Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate. Student's *t*-test was used to compare the means and medians between 2 groups. The Mantel-Haenszel odds ratio (OR) and associated P values were obtained for the variables of interest according to the children's hearing-loss status or percentage of culture-positive visits (categorized as ≤50%, 51%–75%, 76%–99%, and 100% in univariate analyses). A two-sided χ^2 test for linear trends was used for variables with more than two ordered categories. To assess the relationship between persistent CMV shedding and delayed hearing loss, we used multivariate logistic regression models with delayed hearing loss as the outcome variable and number of culture-positive visits or age at last culture-positive visit as the main exposure variables. To account for the wide variation in number of visits and length of follow-up, we limited these analyses to children with at least 3 viral culture visits and we censored follow-up at 96 months. The 21 children with delayed hearing loss who met these inclusion criteria were matched 3-to-1 by age of last hearing evaluation (within 4 months) with 63 randomly selected children who did not develop hearing loss. The variables symptomatic at birth and number of viral culture visits were included as potential confounders; age at last hearing evaluation was included in the models because it was the matching variable. Several variables (*e.g.*, referral from outside hospital, private insurance, private prenatal care, white race) were not included in the multivariate model because they were strongly correlated with and believed to be markers for symptomatic infection at birth. Nine children received ganciclovir during the study. Four of these had hearing loss at birth, leaving only 5 who could be part of the multivariate analyses (1 who developed delayed hearing loss and 4 who did not). Because of its rarity, we did not include the use of ganciclovir as a potential confounding variable.

To assess rates of delayed hearing loss among children with congenital CMV infection, we stratified observed rates by whether a child was asymptomatic or symptomatic at birth, as this was the strongest predictor of delayed hearing loss. To ensure that the hearing loss was in fact delayed (i.e., not present at birth) and to ensure an adequate sample size in each age stratum, we limited the calculation of observed rates to children between 6 and 95 months of age. To obtain the expected number of cases of delayed hearing loss that would have been detected if all children had had complete follow-up, we multiplied age-specific observed rates of hearing loss by age-specific person-years of missing follow-up.

RESULTS

Viral culture

Of 2441 patient-visits with viral cultures, 1525 (62.5%) were CMV positive in saliva or urine or both. Of 1837 saliva cultures, 849 (46.2%) were positive, and of 1816 urine cultures, 1181 (65%) were positive. Among visits where both urine and saliva were cultured, if the saliva was positive, the urine was almost always positive (91%); however, if the urine was positive, the saliva was positive only 63% of the time (Table 1). Prevalence of CMV culture-positivity in any specimen was approximately 50% by the 3rd birthday and approximately 5% after the 7th birthday (Figure 1, Supplemental Digital Content 1, http://links.lww.com/A959). Intermittent shedding occurred in 164 (28%) children (Figure 2, Supplemental Digital Content

2, http://links.lww.com/A960). None of the variables we evaluated was significantly associated with persistent CMV shedding as measured by the percentage of culture-positive visits (Table 2, Supplemental Digital Content 3, http://links.lww.com/A961). In particular, we found no clear trend between being symptomatic at birth and having persistent CMV shedding (Figure 1, Supplemental Digital Content 1, http://links.lww.com/A959).

Hearing loss

At the end of follow-up, 465 children had normal hearing, 77 had hearing loss at birth, and 38 had delayed hearing loss. In univariate analyses, factors significantly associated with hearing loss at birth included symptomatic CMV infection at birth (OR=9.3), white race (OR=2.7), low birthweight (OR=2.7), being referred by an outside hospital (OR=7.0), the mother being married (OR=2.5), having private insurance (OR=2.0), having private prenatal care (OR=3.3), and having longer follow-up (*i.e.*, more hearing evaluations and viral culture results) (Table 3). Factors significantly associated with delayed hearing loss included symptomatic CMV infection at birth (OR=6.9), having been referred to the study by an outside hospital (OR=4.3), and having longer follow-up (Table 3). There was no obvious association between persistent CMV shedding and delayed hearing loss (Figure 1, Supplemental Digital Content 1, http://links.lww.com/A959 and Figure 2, Supplemental Digital Content 2, http://links.lww.com/A960); in fact, a number of children were culture-negative for months and even years before being diagnosed with delayed hearing loss (Figure 2, Supplemental Digital Content 2, http://links.lww.com/A960). However, in multivariate analyses there was a modest yet significant association between age at last culture-positive visit and delayed hearing loss (Table 4A). The odds ratio of 1.05 per month suggests that a child who sheds one year longer than another child has a 1.6 higher odds (95% CI 1.1–2.0) of having delayed hearing loss. No significant association was found between number of culture-positive visits and delayed hearing loss (Table 4B).

For the 424 children who were free of hearing loss at age 6 months, overall observed rates of initial diagnosis of hearing loss (*i.e.*, delayed hearing loss) were 0.79 per 100 person-years for children asymptomatic at birth and 4.29 per 100 person-years for children symptomatic at birth (Table 5). If the entire cohort of congenitally infected children had been followed from age 6 months until their 8th birthday, the expected number of additional cases of delayed hearing loss that would have been detected was ~10 (calculated value, 9.75) among children asymptomatic at birth and ~12 (calculated value, 11.99) among children symptomatic at birth (Table 5). Thus, in the cohort of 335 asymptomatic children, we would expect 23 (6.9%) cases of delayed hearing loss by age 8, and in the cohort of 89 symptomatic children, we would expect 30 (33.7%) cases of delayed hearing loss by age 8. This does not include any cases of delayed hearing loss that occur between birth and 6 months of age.

DISCUSSION

We found that the strongest predictor of delayed hearing loss was the presence of symptoms at birth. Children who passed initial audiologic examinations but who had CMV-related symptoms at birth (*e.g.*, jaundice, petechiae, microcephaly, etc.) were nearly 6 times more likely to develop hearing loss than children who were asymptomatic at birth.

Another important finding was that longer duration of viral shedding (as measured by age at last culture-positive visit) may be a predictor of delayed hearing loss. This raises the hypothesis that ongoing viral replication could play a role in the development of delayed hearing loss. However, there are no data on whether peripheral CMV shedding is linked to CMV replication in the inner ear. They could occur independently. Furthermore, the measure of viral shedding —age at last positive-culture visit—was an imperfect measure of persistent shedding. Nearly 1/3 of children shed CMV intermittently. Thus, those with older ages at their last positive visit

may not have been shedding regularly in the interim, making it less likely that persistent CMV shedding played a role in the development of hearing loss. Finally, the children were not enrolled in studies designed to evaluate the association between viral shedding and delayed hearing loss. As a result, there was wide variation in the number of visits and length of follow-up, complicating the analyses and leading to a relatively small sample for the multivariate analysis. Nevertheless, these complications were minimized by the matching scheme, controlling for confounding, and restriction to children with at least 3 visits and no more than 8 years of follow-up.

Our results differed from a previous study that evaluated persistent CMV shedding and hearing loss. In a smaller study, Noyola et al.[17] found that children who shed CMV for a shorter length of time were more likely to have hearing loss and progressive hearing loss. Those study results may differ from ours because Noyola and colleagues did not analyze delayed hearing loss separately, but instead included it in the category of progressive hearing loss. Furthermore, they did not show the ages at which hearing loss occurred, so that one could not determine whether the shorter duration of CMV shedding actually preceded hearing loss in individual children.

Our multivariate analyses suggest that delayed hearing loss may be associated with persistent CMV shedding during childhood. Other factors may also be important. Viral factors that are present in utero (e.g., high viral load in amniotic fluid) or shortly after birth (e.g., high viral load at birth) may be linked to delayed hearing loss. This would be consistent with results showing that ganciclovir treatment in the 6 weeks following birth seems to prevent some delayed or progressive hearing loss among symptomatic children with CNS involvement.[13] High CMV viral loads at birth have been associated with clinical abnormalities at birth (*i.e.*, symptomatic congenital CMV infection)[14,16,19,20] and with hearing loss.[14] The effect of persistently high viral loads on delayed hearing loss, however, is not known. For the follow-up visits which constituted our study, we did not have measures of CMV viral load and so were unable to assess this potential association. Localized CMV shedding in the ear might also be a predictor of delayed hearing loss, but is impractical to measure. Nevertheless, some researchers have had success in detecting CMV in perilymph fluid during cochlear implant surgery.[21] Alternatively, non-viral factors such as inflammation related to CMV infection could play a role in delayed and progressive hearing loss. Due to lack of data, however, these theories remain speculative. As has been demonstrated previously,[6,9] children with congenital CMV infection who are symptomatic at birth but who test normal on hearing exams are at especially high risk of developing delayed hearing loss. Even though their symptoms often did not include serious, central nervous system impairments, these children were approximately 5–6 times more likely to develop delayed hearing loss, indicating that they need regular audiologic monitoring. Nevertheless, asymptomatic children, who also have much higher rates of delayed hearing loss than the general population, should benefit from regular audiologic monitoring as well.[7]

In this study we were able to calculate rates of the development of delayed hearing loss. Children with normal hearing at 6 months of age developed hearing loss at the rate of nearly 1% per year if they were asymptomatic at birth and over 4% per year if they were symptomatic at birth. Their cumulative risk by age 8 was substantial—6.9% and 33.7% for populations of asymptomatic and symptomatic children, respectively. Cumulative risk of delayed hearing loss may be even higher, since these numbers do not include children whose newborn hearing test was normal but who developed hearing loss within the first 6 months. It is important to note, however, that some of the children will have mild hearing loss (e.g., thresholds <40 dB) which may not reach clinical significance.[6]

With this large sample of congenitally infected children we were able to confirm several observations about the dynamics of CMV shedding that were observed in smaller studies. First, CMV was found more frequently in urine than in saliva, confirming that, when available, urine is the best specimen for diagnosis of shedding. Others have found that viral loads are also higher in urine than in saliva or blood.[22] Second, intermittent CMV shedding is relatively common[17] and may be the result of viral reactivation or reinfection with a different strain.[23] Third, the frequency of CMV shedding decreases substantially with age,[24] indicating that younger children are a key source of infection, and that pregnant women should use careful hygienic precautions when they are exposed to younger children.[25]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Viral culture findings for urine and saliva for all follow-up visits of the 580 children with congenital cytomegalovirus (CMV) infection (N=2441)

	Saliva Cultures				
	Negative	**Positive**	**Contaminated**	**No Culture**	**Total**
Urine Cultures					
Negative	319 (12.9%)*	25 (1.1%)	4 (0.2%)	201 (8.2%)	549 (22.3%)
Positive	253 (10.3%)	505 (20.5%)	38 (1.5%)	385 (15.6%)	1181 (48.0%)
Contaminated	22 (0.9%)	25 (1.1%)	21 (0.8%)	18 (0.7%)	86 (3.5%)
No Culture	288 (11.7%)	294 (11.9%)	43 (1.7%)	0 (0.0%)	625 (25.6%)
Total	882 (35.8%)	849 (34.5%)	106 (4.3%)	604 (24.7%)	2441 (100%)

* Percentages are calculated with the total number of viral cultures (N=2441) as the denominator.

TABLE 3

Comparison of characteristics of children who had congenital cytomegalovirus (CMV) infection stratified by hearing loss status

	Normal hearing (Referent)		Hearing loss at birth		OR* (95% CI)	Delayed hearing loss		OR (95% CI)
Infant characteristics								
Type of neonatal infection								
Asymptomatic	380	(81.7)	25	(32.5)	1	15	(39.5)	1
Symptomatic	85	(18.3)	52	(67.5)	9.3 (5.5–15.8)	23	(60.5)	6.9 (3.4–13.7)
Sex								
Female	216	(46.5)	35	(45.5)	1	22	(57.9)	1
Male	249	(53.5)	42	(54.5)	1.0 (0.6–1.7)	16	(42.1)	0.6 (0.3–1.2)
Race								
Black	332	(71.4)	37	(48.1)	1	25	(65.8)	1
White	133	(28.6)	40	(51.9)	2.7 (1.7–4.4)	13	(34.2)	1.3 (0.6–2.6)
Gestational age								
Full term (≥38wks)	341	(73.3)	51	(66.2)	1	24	(63.2)	1
Preterm (<38wks)	124	(26.7)	26	(33.8)	1.4 (0.8–2.3)	14	(36.8)	1.6 (0.8–3.2)
Low birthweight								
≥2500gms	356	(76.6)	42	(54.5)	1	26	(68.4)	1
<2500gms	109	(23.4)	35	(45.5)	2.7 (1.7–4.5)	12	(31.6)	1.5 (0.7–3.1)
Mode of study enrollment								
Screened at UAB	391	(84.1)	33	(42.9)	1	21	(55.3)	1
Referral from other hosp.	74	(15.9)	44	(57.1)	7.0 (4.2–11.8)	17	(44.7)	4.3 (2.2–8.5)
Maternal characteristics								
Marital status								
Single	313	(67.3)	35	(46.1)	1	25	(65.8)	1
Married	152	(32.7)	41	(53.9)	2.5 (1.4–3.3)	13	(34.2)	1.1 (0.5–2.0)
Insurance status								
Medicaid or none	351	(76.0)	45	(59.2)	1	29	(76.3)	1
Private	111	(24.0)	31	(40.8)	2.0 (1.3–3.3)	9	(23.7)	1.0 (0.5–2.0)
Prenatal care								
Health department or none	351	(75.6)	35	(46.1)	1	26	(68.4)	1
Private	113	(24.4)	41	(53.9)	3.3 (2.0–5.0)	12	(31.6)	1.4 (0.7–3.3)

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	Normal hearing (Referent)		Hearing loss at birth		OR* (95% CI)	Delayed hearing loss		OR (95% CI)
Type of maternal infection								
Recurrent infection	98	(40.3)	7	(29.2)	1	6	(37.5)	1
Primary infection	145	(59.7)	17	(70.8)	1.6 (0.7–4.1)	10	(62.5)	1.1 (0.4–3.2)
Viral culture characteristics								
Percent of follow-up visits that were culture-positive								
≤50% (referent)	137	(29.5)	26	(33.8)	1	13	(34.2)	1
51% – 75%	73	(15.7)	18	(23.4)	1.3 (0.7–2.5)	14	(36.8)	2.0 (0.9–4.5)
76% – 99%	30	(6.5)	10	(13.0)	1.8 (0.7–4.0)	2	(5.3)	0.7 (0.2–3.3)
100%	225	(48.4)	23	(29.9)	0.5 (0.3–1.0)	9	(23.7)	0.4 (0.2–1.0)
					P-value			*P*-value
Median no. of viral follow-up visits (range)	3 (1–14)		5 (1–14)		<0.001	6 (1–6)		<0.001
Mean percentage of positive culture visits for all patients (% ± SD)	0.74 ± 0.30		0.65 ± 0.32		0.02	0.64 ± 0.28		0.03
Hearing loss characteristics								
Median no. of hearing evaluations (range)	5 (1–19)		10 (1–42)		<0.001	13 (5–29)		<0.001
Mean duration of hearing follow-up (mo ± SD)	63.3 ± 47.4		76.7 ± 40.9		0.01	102.7 ± 51.1		<0.001

*OR is defined as the odds of hearing loss in one group compared to the odds of hearing loss in the referent group.

OR, odds ratio; CI, confidence interval; UAB, University of Alabama at Birmingham; SD, standard deviation.

TABLE 4

Logistic regression modeling of the association between persistent positive CMV cultures and delayed hearing loss*

	Delayed hearing loss OR (95% CI)
A	
Age at last culture-positive visit	1.05 (1.01–1.08)[b]
Type of neonatal infection	
Asymptomatic	1
Symptomatic	5.9 (1.8–18.9)
Age at last hearing evaluation	0.99 (0.96–1.01)†
Number of viral culture visits	0.87 (0.59–1.30)‡
B	
Number of culture-positive visits	1.05 (0.66–1.69)‡
Type of neonatal infection	
Asymptomatic	1
Symptomatic	4.4 (1.5–12.6)
Age at last hearing evaluation	1.00 (0.98–1.02)†
Number of viral culture visits	0.96 (0.64–1.43)‡

*The 21 children with delayed hearing loss were matched 3-to-1 by age at last hearing evaluation with 63 randomly selected children who did not develop hearing loss. Model A used age at last culture-positive visit as the exposure variable. Model B used number of culture-positive visits as the exposure variable. The other covariates were the same for the two models.

†Comparing 1-month age differences.

‡Comparing 1-visit differences.

CMV, cytomegalovirus; OR, odds ratio; CI, confidence interval.

TABLE 5

Rates of delayed hearing loss and estimated underdiagnosis of delayed hearing loss among children born with congenital cytomegalovirus (CMV)

	Observed cases of delayed HL		Children free of HL at beginning of follow-up*		Observed rates of delayed HL (per 100 children per year)			Number of children who missed follow-up during time period		Expected cases of delayed HL not diagnosed due to lack of follow-up until age 8†		
Age in months	Asym.	Sym.	Asym.	Sym.	Asym.	Sym.	All	Asym.	Sym.	Asym.	Sym.	All
6–11	0	5	335	89	0	11.24	2.36	37	15	0	0.84	0.84
12–23	0	3	305	78	0	3.85	0.78	62	20	0	0.74	0.74
24–35	4	1	283	73	1.41	1.37	1.40	92	30	1.30	0.39	1.69
36–47	1	3	255	67	0.39	4.48	1.24	114	34	0.44	1.43	1.87
48–59	5	0	235	59	2.13	0	1.70	143	40	3.01	0	3.01
60–71	1	3	176	44	0.57	6.82	1.82	162	45	0.90	2.84	3.74
72–83	1	2	135	31	0.74	6.45	1.81	225	58	1.62	3.34	4.96
84–95	1	1	96	23	1.04	4.35	1.68	255	65	2.48	2.41	4.89
Total	13	18	1652.5 P-Y	419.5 P-Y	0.79	4.29	1.50			9.75	11.99	21.74
95% CI					0.42–1.35	2.54–6.78	1.02–2.12			5.18–16.66	7.10–18.95	14.78–30.73

*Also had hearing follow-up at least until the end of the last month of the age category.

†Computed as observed rates in a given age group multiplied by the number of children who missed follow-up during the time period. For most age groups the number of expected cases was slightly less than the observed rate multiplied by the missed follow-up time because, for calculations of expected cases at older ages, expected cases occurring at younger ages had to be subtracted from the number of children who missed follow-up.

HL, hearing loss; Asym., child asymptomatic at birth; Sym., child symptomatic at birth; CI, confidence interval; P-Y, person-years.