Published in final edited form as:

Pediatr Infect Dis J. 2016 August ; 35(8): 924–926. doi:10.1097/INF.0000000000001194.

Clinical Predictors of Sensorineural Hearing Loss and Cognitive Outcome in Infants with Symptomatic Congenital Cytomegalovirus Infection

Swetha G. Pinninti, MD¹, Mackenzie D. Rodgers, MD², Zdenek Novak, MD, PhD, MSHI³, William J Britt, MD³, Karen B. Fowler, DrPH³, Suresh B. Boppana, MD³, and Shannon A. Ross, MD, MSPH³

¹University of Nebraska Medical Center/Children's Hospital and Medical Center, Omaha, Nebraska

²Brookwood Medical Center, Birmingham, Alabama

³University of Alabama at Birmingham, Birmingham, Alabama

Abstract

The objective of this study was to determine newborn clinical findings predictive of adverse clinical outcomes in infants with symptomatic congenital cytomegalovirus (cCMV) infection. Of 160 infants, significantly more children with central nervous system (CNS) involvement had sensorineural hearing loss (SNHL) ($p = 0.0007$) and an IQ < 70 ($p < 0.0001$) compared with infants with transient findings or only a petechial rash.

Keywords

cytomegalovirus; sensorineural hearing loss; predictors; cognitive outcome

Background

Congenital cytomegalovirus (cCMV) infection is a leading non-genetic cause of sensorineural hearing loss (SNHL) and neurologic disabilities in the U.S.(1–3). Of the 10–15% of infected infants with clinical evidence of congenital infection (symptomatic), 40–60% develop sequelae including SNHL, cerebral palsy, neurodevelopmental delay and retinitis(2). The risk factors for SNHL and other sequelae in children with cCMV are unknown. Identification of predictors of outcome will permit appropriate counseling, judicious resource utilization and selection of infants who would benefit most from anti-viral therapy. Since the presentation of symptomatic cCMV is highly variable, we explored

Corresponding Author: Swetha G. Pinninti, M.D., Assistant Professor, Department of Pediatrics, University of Nebraska Medical Center/Children's Hospital and Medical Center, 8200 Dodge Street, Omaha, NE - 68114, swetha.pinninti@unmc.edu.

Potential conflicts of interest: All authors report no conflict of interest relevant to this manuscript.

Presentations: These findings were presented in part at the Infectious Diseases Society of America annual meeting, IDWeek, October 8–12, 2014 in Philadelphia, PA.

whether symptomatic infants could be stratified for their risk of sequelae based on clinical presentation at birth.

Materials and methods

Patient population

The study population consisted of 174 infants with cCMV enrolled in longitudinal follow-up at University of Alabama at Birmingham (UAB) between 1980 and 2002. The newborn clinical findings, diagnosis of cCMV and long-term outcome in these infants has been described previously(4).

Categorization of infants with symptomatic cCMV

Since the involvement of the central nervous system (CNS) at birth is associated with permanent deficits, infants with microcephaly, seizures, lethargy/hypotonia, poor suck and/or neuroimaging findings (intracerebral calcifications, ventricular dilatation, white matter attenuation or cortical atrophy) with or without other findings were categorized as the CNS group. In contrast, the involvement of hepatobiliary and hematopoietic systems almost always resolves without long-term complications. Therefore, infants with jaundice, purpura, or hepatosplenomegaly on physical examination, elevated aspartate aminotransferase or thrombocytopenia with or without petechial rash and without CNS involvement were considered as the transient findings group. Infants with only a petechial rash without other findings comprised the third group.

Audiologic Follow-up

Study children were followed with serial audiologic and neurologic examinations performed as described previously(5). Criteria for congenital, late-onset SNHL, and degree of SNHL have been described previously (5, 6). The study children were classified into two groups based on the degree of SNHL(7). The first group included infants with normal hearing or mild SNHL (unilateral SNHL of any severity and mild bilateral SNHL in the better ear). Children with bilateral moderate, severe or profound SNHL who would benefit from hearing aids and cochlear implantation were included in a second group.

Neurodevelopmental follow up

Developmental and intellectual evaluations were administered using standard psychometric tests appropriate for age, perceptual function, and physical abilities as described (4, 5, 8).

Statistical analysis

The newborn findings and follow-up data were maintained in SAS 9.3 for Windows data sets (SAS Institute, Cary, North Carolina). The incidence and severity of congenital and late-onset SNHL and cognitive deficits were compared between the three groups. Odd ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression. Statistical significance was determined using χ^2 or Fisher's exact test, where appropriate.

Results

Of the 174 infants with symptomatic cCMV, 14 infants received anti-viral therapy and were excluded from the analysis. Of the remaining 160 infants, 84 (52.5%) had evidence of CNS involvement, 53 (33.1%) presented with transient symptoms and 23 (14.4%) had petechiae alone. The average length of follow-up was 4.6 ± 3.8 years. Neuroimaging was performed in 56/155 (36.1%) infants (14/53 in the transient group and 42/79 in the CNS group). Infant gender, maternal age, marital status and insurance status were not different between the three groups. Significantly more infants in the CNS and the transient symptoms groups received prenatal care in a private clinic ($p=0.01$) and were referred from other facilities because of clinical findings suggestive of cCMV ($p<0.001$).

Hearing outcome data was available in 155/160 (96.9%) children, and of those 45.8% (71/155) had SNHL. Figure 1 shows the incidence of congenital and late onset SNHL according to their presentation at birth. Of the 71 children with SNHL, 49 (69.1%) had congenital SNHL and 22 (30.9%) developed late-onset loss. Significantly more children in the CNS group had SNHL (46/79, 58.2%) compared with those with transient symptoms (20/53, 37.7%) or only petechiae (5/23, 21.7%, $p=0.0007$). Compared with infants with only petechiae, those in the CNS group were five times (OR=5.1; 95% CI: 1.6–18.9) more likely and those in the transient symptoms group were twice (OR=2.2; 95% CI: 1.1–4.7) as likely to have SNHL. The frequency of late-onset SNHL did not differ between the groups. Sixteen percent (95% CI: 9.4%–25.5%) of infants in the CNS group developed late-onset SNHL, which was similar to the transient symptoms group (13.2%; 95% CI: 5.4–24.5) and the petechiae only group (8.7%; 95% CI: 1.1–28.0).

Although the majority of children with SNHL in the CNS (33/46, 71.7%) and transient symptom groups (15/20, 75%) had bilateral SNHL compared with only one of five children in the petechiae alone group, this difference was not statistically significant ($p=0.07$). Further deterioration (progression) of SNHL was observed in significantly more children in the transient symptoms (16/20, 80%) and petechiae only (4/5, 80%) groups compared to the CNS group (20/46, 43.5%; $p=0.008$). None of the 5 children with SNHL in the petechiae only group had moderate-profound loss compared with 45% of the transient symptoms group (9/20) and 52% of the CNS group (24/46; $p=0.06$).

Cognitive outcome data was available in 88 children and of these, 35% (31/88) were found to have IQ<70. Significantly more children with CNS involvement had IQ < 70 (23/39, 59%) than those with transient symptoms (8/39, 20%, $p<0.0001$). None of the ten children in the petechiae only group who underwent psychometric testing had IQ < 70.

Discussion

In this large cohort of children with symptomatic cCMV, we demonstrate that the risk of SNHL and adverse cognitive outcome varies depending on the clinical presentation at birth. The findings show that moderate to profound SNHL and poor cognitive outcome are more frequent in children with CNS involvement at birth.

Natural history studies of children with symptomatic cCMV have reported varying rates of sequelae, from 35%–100% (5, 9–11). Previous studies that examined individual clinical findings at birth as predictors of SNHL and neurodevelopmental outcome in symptomatic cCMV were inconclusive (6, 12, 13). The data from published studies show that microcephaly, chorioretinitis, and neuroimaging abnormalities in the newborn period were associated with poor intellectual outcome (12, 13). In a study that included many of the children in this report, SNHL was associated with the presence of petechiae at birth and not evidence of CNS involvement(6). However, the frequency of adverse sequelae and the degree of SNHL was not analyzed according to the organ system involvement at birth.

A possible explanation for higher incidence of SNHL and poor cognitive outcome in the CNS group is that the infection in early gestation leading to widespread virus dissemination *in utero* and more damage thereby increases the risk for adverse outcomes. Studies have found that children with cCMV following a first trimester maternal infection were more likely to have sequelae, especially SNHL(14). The finding of a significantly lower risk for SNHL and cognitive deficits in infants with petechial rash alone supports the view that virus dissemination is important in determining long-term outcome. However, this notion is speculative without conclusive evidence at this time. We did not find an association between clinical presentation at birth and late onset SNHL, suggesting a different pathogenic mechanism for SNHL occurring after birth. Significantly more children with transient findings and petechial rash alone experienced progression of SNHL compared with the CNS group, likely due to infection occurring later in gestation leading to milder presentation at birth with further deterioration of hearing during early childhood.

Our findings provide more precise data on the risk for sequelae according to the presentation at birth and allows for appropriate counseling of parents. While the majority of infants with severe disease in the newborn period will have SNHL, it is pertinent to note that infants with findings of any severity continue to be at-risk for late-onset and/or progressive SNHL emphasizing the importance of continued monitoring.

Studies have estimated that approximately 10–15% of asymptomatic children will develop SNHL(15), which is similar to the 22% (95% CI: 7.5–43.7%) of children with only petechiae in this study. Our findings indicate that the clinical presentation of cCMV in the newborn period is a continuum of disease expression and the risk for SNHL increases with increasing severity of disease at birth. Asymptomatic infants are at one end of the spectrum of cCMV disease, and have the lowest risk for SNHL, with the risk of SNHL increasing as the severity of disease presentation increases in the newborn period [asymptomatic (10–15%) < petechiae only (22%) < transient (37%) < neurologic (59%)].

The limitations of this study include the retrospective analysis of the data and that not all study subjects underwent neuroimaging, laboratory evaluation and cognitive testing. Moreover, the sample sizes of the children in the petechiae only group with SNHL (n=5) and cognitive outcome data (n=10) were small and not powered to detect subtle differences. Despite these limitations, this study includes a large cohort of children with symptomatic cCMV and demonstrates significant differences in outcomes based on clinical presentation at birth.

In conclusion, in infants with symptomatic cCMV, those with evidence of CNS involvement at birth are at significantly higher risk for SNHL and cognitive deficits than those with transient symptoms or a petechial rash suggesting a direct relationship between the severity of disease at birth and the risk for adverse outcomes.

Acknowledgments

Funding: Funded in part by the grants from the National Institutes of Health (5-P01-HD-10699 [to W.B., K.F.], 5-R01-DC-02139 [to S.B., K.F.], 5-P01-A1-43681 [to S.B., W.B., K.F.], and M01-RR-00032).

References

1. Morton CC, Nance WE. Newborn hearing screening--a silent revolution. *N Engl J Med*. 2006; 354:2151–2164. [PubMed: 16707752]
2. WJ, B. Cytomegalovirus. In: Remington, JSKJ.; Wilson, CB.; Nizet, V.; Maldonado, Y., editors. *Infectious Diseases of the fetus and newborn infant*. Philadelphia: Elsevier Saunders; 2011.
3. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006; 35:226–231. [PubMed: 16386462]
4. Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2014; 164:855–859. [PubMed: 24433826]
5. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol*. 2000; 11:283–290. [PubMed: 10821506]
6. Rivera LB, Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Pediatrics*. 2002; 110:762–767. [PubMed: 12359792]
7. Davis H. Guide for the classification and evaluation of hearing handicap in relation to the international audiometric zero. *Trans Am Acad Ophthalmol Otolaryngol*. 1965:740–751. [PubMed: 14345779]
8. 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; 326:663–667. [PubMed: 1310525]
9. Williamson WD, Desmond MM, LaFevers N, Taber LH, Catlin FI, Weaver TG. Symptomatic congenital cytomegalovirus. Disorders of language, learning and hearing. *Am J Dis Child*. 1982; 136:902–905. [PubMed: 6289657]
10. Townsend CL, Forsgren M, Ahlfors K, Ivarsson SA, Tookey PA, Peckham CS. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. *Clin Infect Dis*. 2013; 56:1232–1239. [PubMed: 23334811]
11. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. 1992; 11:93–99. [PubMed: 1311066]
12. Noyola DE, Demmler GJ, Nelson CT, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2001; 138:325–331. [PubMed: 11241037]
13. Conboy TJ, Pass RF, Stagno S, et al. Early clinical manifestations and intellectual outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr*. 1987; 111:343–348. [PubMed: 2442337]
14. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. Hearing loss in children with congenital cytomegalovirus infection in relation to the maternal trimester in which the maternal primary infection occurred. *Pediatrics*. 2008; 122:e1123–e1127. [PubMed: 19047212]

15. 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; 130:624–630. [PubMed: 9108862]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.
Sensorineural hearing loss in children with symptomatic congenital CMV infection according to clinical findings in the newborn period