Insight Into Long-term Neurodevelopmental Outcomes in Asymptomatic Congenital CMV Infection

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In this issue of *Pediatrics*, Lopez et al[1] describe findings from a long-term follow-up study to determine the intellectual outcomes and academic performance of children with asymptomatic congenital cytomegalovirus infection (cCMV). cCMV is the most common congenital infection and is a leading nongenetic cause of sensorineural hearing loss (SNHL) and neurodevelopmental disability.[2–4] In the United States, the number of infants who develop adverse hearing and neurodevelopmental outcomes from cCMV approaches those from Down syndrome and exceeds those from the fetal alcohol syndrome, spina bifida, and childhood infections (including HIV and *Haemophilus influenzae* type B meningitis before the vaccine era).[5] Most infants (85%–90%) with cCMV have no detectable clinical abnormalities at birth (asymptomatic or subclinical cCMV), and ∼10% to 15% of these children have varying degrees of SNHL.[3] Intellectual outcomes and academic performance in this group of children have not been well defined.[6] This gap in our understanding is due to the fact that most asymptomatic infants are not recognized at birth. In addition, a retrospective diagnosis of cCMV is difficult because positive cytomegalovirus (CMV) results from specimens obtained after 3 weeks of age could be from postnatally acquired infection.

The study by Lopez et al[1] includes a systematic evaluation of children with asymptomatic cCMV by measuring their cognitive outcomes and academic performance through the first 18 years of age. The authors did not find significant differences in the scores for verbal and nonverbal intelligence, expressive vocabulary, and academic performance in math and reading between the controls and the children infected with CMV with and without hearing loss. The findings reported by Lopez et al[1] confirm previous reports that included smaller numbers or shorter duration of follow-up or both.

Kashden et al[7] monitored 204 children with asymptomatic cCMV and 177 uninfected siblings for intellectual outcome and found no difference in the intellectual outcome between children with asymptomatic cCMV and uninfected siblings. Although that study included a larger number of children with cCMV, the duration of follow-up was much shorter than the Lopez et al[1] study. The average age at testing was 4 years and 6 years for children with asymptomatic infection and the control group, respectively. Lopez et al[1] measured neurodevelopmental outcomes in 91 children with asymptomatic cCMV and 42 unmatched controls. The study children were assessed at least once during infancy, preschool, elementary, middle, and high school years for intelligence, language skills, and academic achievement. The outcomes were compared among asymptomatic children with SNHL diagnosed before 2 years of age,

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those with normal hearing or SNHL after 2 years of age, and the control group. An additional strength of the study by Lopez et al[1] is their use of growth-curve modeling to analyze the trends in scores of various neurodevelopmental measures over time.

Although full-scale intelligence and receptive vocabulary scores were lower in children with SNHL when compared with controls, these differences were not statistically significant. However, only 11 children with asymptomatic infection who developed SNHL before 2 years of age were included in the study. Therefore, it is possible that the differences could have reached a statistically significant level if more children with SNHL were included in the study.

A challenge for longitudinal studies in which researchers define outcomes is the appropriate selection of controls because the controls should be as similar as possible to the cases with respect to previous exposures. The control children studied by Lopez et al[1] were born within 6 days of the infants who tested positive for CMV but were not matched for demographic characteristics of the group of congenitally infected children. In addition, the majority of the cases and controls were born to women of medium or high socioeconomic status (SES) and who had at least some college education. As the authors stated, their study findings may not be generalizable to other populations with lower SES and education levels. Therefore, it will be important to confirm the findings of this study in populations in which children come from families with lower SES to evaluate whether similar findings would be identified. There are many confounding factors that may influence a child's intellectual development. For example, higher-SES parents may have access to more material resources, such as healthy food and medical care; also, better educated parents may be better able to stimulate their children's development. For children from lower-SES families, factors such as family stress, neighborhood environment, greater exposure to environmental toxins, or poor nutrition may impact their development. Ideally, a study in which researchers match sibling controls and can adjust for the impact of family and neighborhood environment on a child's intellectual development is needed to measure whether asymptomatic cCMV has an independent effect on a child's later neurodevelopmental outcome.

Lopez et al[1] provide encouraging findings and new insights on the long-term neurodevelopmental outcomes in children with asymptomatic cCMV. This information is helpful in defining the disease burden from this important prenatal infection. In addition, it is reassuring that most children with asymptomatic cCMV are not at increased risk for disabilities from poor intellectual outcomes and academic performance.

ABBREVIATIONS

cCMV: congenital cytomegalovirus infection
CMV: cytomegalovirus
SES: socioeconomic status
SNHL: sensorineural hearing loss

REFERENCES

1. Lopez AS, Lanzieri TM, Claussen AH, et al. Intelligence and academic achievement with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 2017;140(5):e20171517
2. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*. 2007;17(4):253–276
3. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006;35(2):226–231
4. Boppana SB, Britt WJ. Synopsis of clinical aspects of human cytomegalovirus disease. In: Reddehase MJ, ed. *Cytomegaloviruses: From Molecular Pathogesis to Intervention*. London, United Kingdom: Caister Academic Press; 2013
5. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol*. 2009;46 (suppl 4):S6–S10
6. Cannon MJ, Grosse S, Fowler KB. The Epidemiology and Public Health Impact of Congenital Cytomegalovirus Infection. In: Reddehase MJ, ed. *Cytomegaloviruses: From Molecular Pathogenesis to Therapy*. Norfok, United Kingdom: Caister Academic Press; 2013:26–48
7. Kashden J, Frison S, Fowler K, Pass RF, Boll TJ. Intellectual assessment of children with asymptomatic congenital cytomegalovirus infection. *J Dev Behav Pediatr*. 1998;19(4):254–259

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