Experts make the case for universal CMV screening

Infectious Diseases in Children, May 2019

Cytomegalovirus, or CMV, is relatively common in the United States, with nearly one in five children infected with the virus by age 5 years. More than half of adults will become infected by age 40 years.

Most people with healthy immune systems develop no signs or symptoms, but neonates are particularly vulnerable to the effects of congenital CMV infection. A review published in *Pediatrics* suggested that one in three children with symptomatic CMV infection and one in 10 asymptomatic children will experience hearing loss. The virus causes severe to profound sensorineural hearing loss in approximately 10% to 20% of all children with hearing loss.

Shannon A. Ross, MD, MSPH, associate professor of pediatrics and microbiology at the University of Alabama, Birmingham, told *Infectious Diseases in Children* that the risk for hearing loss increases with neurologic involvement.

“Symptomatic children with neurologic involvement, including microcephaly, calcifications or other abnormalities on their neuroimaging, are also more likely to have hearing loss and other developmental delays,” Ross said. “Another symptom that we see with congenital CMV is retinitis, or inflammation in the retinas. This is more common in children with symptomatic infection.”

David W. Kimberlin

Signs and symptoms that point toward CMV infection — including jaundice from hyperbilirubinemia, an enlarged or poorly functioning liver, and microcephaly — warrant further testing. However, 85% to 90% of neonates with congenital infection are “completely asymptomatic at birth,” according to **David W. Kimberlin, MD,** professor of pediatrics, vice chair for clinical and translational research and co-director of the division of pediatric infectious diseases at the University of Alabama at Birmingham.

“You would not know that they were infected unless you were specifically screening for the virus,” Kimberlin said.

Gail Demmler-Harrison

Early detection of hearing loss is crucial, but controversy surrounds the best approaches to identify children affected by CMV. **Gail Demmler-Harrison, MD,** professor of pediatrics in the section of infectious diseases at Baylor College of Medicine and an attending physician in pediatric infectious diseases at Texas Children's Hospital, said in an interview that although screening all babies for CMV infection, or universal screening, has been considered for decades, most institutions still opt for a targeted approach. This strategy tests infants for CMV infection if they do not pass their newborn hearing screen.

Many experts — including Demmler-Harrison, Kimberlin and Ross — favor a more universal approach in which every newborn is tested for CMV, along with other conditions in the neonatal care setting.

Screening approaches

In 2013, Utah became the first state to require hearing-targeted CMV screening for all infants who fail their newborn hearing tests. Since then, 16 states have either proposed or passed legislation requiring CMV education, newborn screening or both, according to the National CMV Foundation.

To this day, no standard exists for screening babies for CMV.

"To my knowledge, outside the research setting, screening every baby is not a universal practice, but it is something those of us in the CMV community feel that we should move forward with," Demmler-Harrison said. "There is a process that has to be done, and we really haven't moved forward on that process for universal CMV screening."

When CMV screening is suggested for infants, three options exist: urinalysis, saliva swabs and dried blood spots.

Authors of a study published in *JAMA* suggested that dried blood spots have gained increasing interest because they are already routinely collected for screening of metabolic disease in all U.S.-born infants. The researchers investigated whether this method of testing, which used PCR assays, could identify infants at a comparable rate to saliva specimens tested by rapid culture. Nearly all infants tested for CMV using saliva were identified (n = 91 of 92 CMV-confirmed infants). In this study, dried blood spots had a sensitivity of only 28.3% (95% CI, 17.4%-41.4%) but a specificity of 99.9% (95% CI, 99.9%-100%). A two-primer dried blood spot PCR assay identified CMV-infected infants with a slightly higher sensitivity — at 34.4% (95% CI, 18.6%-53.2%) — and with the same specificity.

“Most studies thus far have shown that the sensitivity of using dried blood spots is poor,” Ross said. “The CHIMES study” — or CMV and Hearing Multicenter Screening Study — “published 40% or less sensitivity, and some older studies have shown better sensitivity. The point to be made about dried blood spots is that not all babies have detectable virus in their blood, so it’s not the best way to diagnose these children.”

Ross said saliva may be a better choice for CMV screening on a larger scale because samples are much easier to collect than a urine sample.

“Urine has not been studied in a large number of infants because of the difficulties of collecting the urine,” she said. “The question is how easy are [the tests] to do in large numbers, and saliva samples are much easier to obtain. It can be done quickly and easily, and you don’t have to put a bag on the infant and wait for them to urinate.”

Research published in *The New England Journal of Medicine* further supported the use of saliva. Boppana and colleagues found that a liquid saliva PCR assay demonstrated 100% sensitivity (95% CI, 95.8%-100%) and 99.9% specificity (95% CI, 99.9% to 100%), with high positive and negative predictive values of 91.4% (95% CI, 83.8%-96.2%) and 100% (95% CI, 99.9%-100%), respectively. Dried saliva samples had a slightly lower sensitivity, at 97.4% (95% CI, 90.8%-99.7%), and the same specificity.

Most infants who are tested for CMV using these methods are targeted through the results of their newborn hearing screening. Although a growing number of states mandate that approach, barriers still exist.

’A logistical issue’

In a study published in *Pediatrics*, Diener and colleagues showed that only 62% of infants in Utah who did not pass their newborn hearing screen were further screened for CMV. Nearly one-quarter of infants did not have a diagnostic hearing evaluation within 30 days of birth. However, more infants underwent diagnostic hearing evaluations in a timely manner after the mandate was enacted, increasing from 56% to 77%.

“It’s one thing to propose a policy or screening program, and it’s another thing to be in the real world and implementing it,” Demmler-Harrison said. “For some, the parents may just decline it for a variety of reasons. For some, it’s just a logistical issue.”

Kimberlin added that the mandate in Utah “adds complexity in requiring targeted screening where complexity did not previously exist,” because prior to this law, screening for CMV was not required. He added that these kinds of programs usually

go through a lot of “growing pains.”

However, many experts question whether targeted screening is the best approach to identify infants at risk for future hearing loss caused by CMV.

“Most babies who are destined to have CMV-associated hearing loss will have normal hearing at birth,” Kimberlin said. “If you have a targeted screening approach, and let’s say that you test every single baby who fails their hearing screening for congenital CMV, you’re still missing most of the babies who are going to go on to develop CMV-associated hearing loss.”

In the CHIMES study, Fowlerand colleagues examined almost 100,000 newborn hearing screenings conducted at seven medical centers between 2007 and 2012. The infants in the study also received CMV testing either through saliva or dried blood spot. The researchers found that 7% of infants who were CMV-positive did not pass their newborn hearing test vs. 0.9% of CMV-negative infants ($P < .0001$). Only two-thirds (65%) of CMV-positive infants who failed their initial hearing screening went on to experience sensorineural hearing loss. Moreover, 3.6% of infants who were infected with CMV but passed their newborn hearing screen later developed sensorineural hearing loss. More than half (57%) of infants with CMV-related sensorineural hearing loss were missed through the targeted approach.

In an effort to promote universal screening, the National CMV Foundation requested that CMV be added to the Recommended Uniform Screening Panel in March of this year. The screening panel includes 35 primary and 26 secondary conditions for which all newborns are screened.

Sara Doutre, National CMV Foundation scientific advisory committee chair and the parent of a child with hearing loss caused by CMV, said in a press release that universal screening may lead to better data about the impact of the virus and could potentially lead to greater investment in vaccine research. Phase 2 trials have been conducted on a CMV vaccine candidate called gB/MF59. One randomized, double-blind, placebo-controlled study of the vaccine has been completed and included approximately 400 girls aged 12 to 17 years. A separate phase 2 study, conducted at the University of Alabama at Birmingham, tested whether the vaccine could prevent women who recently gave birth from being infected between pregnancies. Ross said the vaccine demonstrated poor efficacy in these trials, but more promising vaccines are currently in development.

Demmler-Harrison said that if the decision was left to her, every newborn would be universally screened for CMV.

"It would alleviate the diagnostic odyssey that many of these babies go through," she said. "You would have a diagnosis in the first days to week of life."

However, she emphasized that targeted screening is a step in the right direction and is better than no screening at all. – *by Katherine Bortz*

References:

Boppana SB, et al. *JAMA*. 2010;doi:10.1001/jama.2010.423.

Boppana SB, et al. *N Engl J Med*. 2014;doi:10.1056/NEJMoa1006561.

CDC. About CMV. https://www.cdc.gov/cmv/overview.html. Accessed April 14, 2019.

CMV Public Health and Policy Conference. Information about Cytomegalovirus (CMV). https://cmv.usu.edu/info.cfm. Accessed April 14, 2019.

Diener ML, et al. *Pediatrics*. 2017;doi:10.1542/peds.2016-0789.

Fowler KB, et al. *Pediatrics*. 2017;doi:10.1542/peds.2016-2128.

Goderis J, et al. *Pediatrics*. 2014;doi:10.1542/pediatrics.2014-

National CMV Foundation. National CMV Foundation nominates congenital CMV for RUSP newborn screening. https://www.nationalcmv.org/resources/blog/april-2019/national-cmv-foundation-nominates-congenital-cmv-f. Accessed April 14, 2019.

National CMV Foundation. Our Programs. https://www.nationalcmv.org/about-us/programs. Accessed April 24, 2019.

For more information:

Gail Demmler-Harrison, MD, can be reached at jmjacome@texaschildrens.org.

David W. Kimberlin, MD, can be reached at dkimberlin@peds.uab.edu.

Shannon A. Ross, MD, MSPH, can be reached at sross@peds.uab.edu.

Disclosures: Demmler-Harrison reports that she received grant money from Merck and Microgen. Kimberlin reports no relevant financial disclosures. Ross reports that she hosted an educational webinar for the Alethia CMV Assay and has consulted for Roche and Merck.