EDITORIAL

Congenital Cytomegalovirus Screening Moves Ahead

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The most common infectious cause of life-long disability in newborns is congenital cytomegalovirus (cCMV) infection. The birth prevalence of cCMV is highly variable globally and is directly proportional to the maternal seroprevalence in the population being examined.[1] The birth prevalence of cCMV is reported to be 0.36% to 2.45% in the US and 0.42% to 0.55% in Canada.[2] Fetal infection with CMV, particularly infection occurring in the first trimester, can injure the developing brain, leading to neuronal migration defects, microcephaly, intracranial calcifications, and other manifestations of end organ damage.[3] A wide range of attendant neurological and neurodevelopmental disabilities can ensue, including cerebral palsy, seizure disorders, developmental delay, visual impairment, and autism spectrum disorders.[4] The most important long-term disability is sensorineural hearing loss (SNHL), occurring in 12.6% of all newborns with cCMV.[5] Importantly, SNHL onset is delayed in 43% of infants with cCMV, and hence cCMV-associated hearing loss, in many cases, will be missed by relying solely on newborn hearing screening. Overall, 20% of SNHL cases at birth and 25% of SNHL cases that occur by age 5 years of age are caused by cCMV.[6]

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Given the disabilities associated with cCMV, why is routine CMV testing not performed as a component of the standard newborn screening panel that is obtained in all infants in the US and Canada? After all, cCMV is more common than all of the other diseases tested for on the newborn screening panel combined.[7] Moreover, the timing of infant diagnostic testing for the CMV virus (usually by polymerase chain reaction [PCR]–based identification of viral DNA) is critical, since the finding of viral shedding beyond the 21st day of life in an infant may reflect postnatal infection, typically acquired by breastfeeding,[8] and not true congenital infection. Thus, there is some degree of urgency regarding the timing of testing that should seemingly make cCMV well suited to universal screening.

Universal cCMV Screening: Fraught With Technical and Ethical Challenges

Although a strong case for newborn CMV testing has been proposed for decades, several factors have limited enthusiasm for universal cCMV screening. First, even though cCMV causes substantial disability for some infants, these disabilities are seen in only approximately 15% of newborns; in fact, most infants with cCMV are asymptomatic at birth and have normal neurodevelopmental outcomes.[9] Thus, in contrast to virtually all of the other diagnoses routinely tested for in newborn screenings, a positive cCMV screen, once confirmed, would represent a disorder only for the 15% to 20% of infants for whom an adverse outcome ensues. Second, there has not been uniform agreement among experts regarding the optimal newborn screening test. Although urine PCR has been considered the gold standard for the diagnosis of cCMV, collection of urine samples is time intensive and hence would be prohibitively costly if performed on all newborns. Since dried blood spots (DBS) collected on filter paper cards during the first week of life are routinely used to conduct biochemical screening tests in centralized laboratories on a state-by-state (or province-by-province) level in the US and Canada, DBS PCR screening for CMV DNA has been an appealing option for universal cCMV screening, since an established infrastructure exists to collect and process samples. However, the CMV and Hearing Multicenter Screening (CHIMES) study,[10] performed in the early 2000s, reported a suboptimal DBS sensitivity of 28.3% to 34.4% for diagnosis of cCMV, considerably dampening enthusiasm for this approach. Third, one of the tenets for adding a universal screening test to the newborn panel is the assumption that a disorder, once identified, is amenable to a therapeutic intervention. Although there are some settings in which antiviral therapy with ganciclovir (or its prodrug, valganciclovir) is recommended for cCMV, such therapy is usually reserved only for symptomatic children: for asymptomatic infants, no antiviral treatment is warranted. For these and other reasons, recommendations published by an American College of Medical Genetics expert group[11] for a core group of 29 newborn screening tests in 2006 did not include any recommendation for inclusion of a cCMV test as a component of a standard newborn testing panel.

Laboratory Advances and Advocacy Efforts Pave the Road Forward for Universal cCMV Screening

Since the CHIMES study[10] of the early 2000s, several developments have dramatically changed the landscape of universal cCMV screening. First, technical advances in DNA purification have improved the diagnostic sensitivity of DBS-based analysis. In an unselected universal cCMV screening study of more than 20 000 newborns between 2016 and 2023 in 6 newborn nurseries in Minnesota, the analytic sensitivity of DBS PCR was compared to that of saliva, and found to be substantially improved compared to the CHIMES study. The DBS sensitivity found in 2 independent laboratories was 73% to 77%, with a combined sensitivity of 86%.[12] Although no enhancement of sensitivity could be demonstrated by digital droplet PCR,[13] it is likely that continued refinement of PCR technologies will further enhance the sensitivity of DBS-based cCMV screening.

A second major factor driving the universal cCMV screening effort in recent years has been advocacy. The spheres of public policy, politics, and parental advocacy have intersected and synergized to make universal cCMV screening a re-

ality in 2 states: Minnesota, where screening commenced in 2023, and Connecticut, where it is projected to begin in 2025. In both cases, screening began through legislative action, which in turn was strongly influenced by parents. The National CMV Foundation in the US and CMV Canada have been instrumental in promoting advocacy that has influenced legislation and raised awareness. Published testimonials from parents, such as *Remedies for Sorrow* by Megan Nix,[14] have had a huge impact, not only with medical professionals but with elected representatives as well. In addition to Minnesota and Connecticut, the state of New York is currently conducting universal cCMV screening, through a study funded by a grant from the National Institutes of Health, and will likely incorporate universal cCMV screening into its portfolio after the pilot study period has ended.

Ontario Sets the Tone and Leads the Way in Universal cCMV Screening

A pivotal study by Dunn et al[15] has demonstrated the feasibility of incorporation of universal cCMV screening into the infrastructure of a provincial (Ontario) health department screening program. The report presents the results of a CMV PCR screening assessment in approximately 550 000 newborns from July 2019 to July 2023. The fact that universal cCMV screening was initiated and successfully implemented during this period is particularly impressive when considered against the backdrop of the COVID-19 pandemic, which intersected this time window. Although the pandemic complicated administration of the CMV screening program, it was nevertheless successfully realized, making Ontario the first governmental jurisdiction in the world to codify a universal cCMV testing program. Of note, the program was initially housed in the Ontario Infant Hearing Program and not in Newborn Screening Ontario. State and provincial hearing programs may represent the best homes for cCMV screening initiatives in light of the fact that the main justification for universal cCMV screening is to monitor for and identify delayed-onset SNHL. The key driving force for universal cCMV screening is to identify infants at risk of delayed-onset SNHL (which would otherwise easily be overlooked), toward the goal of optimizing childhood speech and language outcomes.

What has Ontario detected to date? Of 565 987 infants born during the screening period described in the article by Dunn et al,[15] 551 034 were screened for cCMV using DBS PCR. Of 689 infants with positive results, 601 had cCMV infection confirmed and completed an evaluation that included identification of CMV via urine PCR, review of symptoms at birth, assessment for intrauterine growth restriction, physical examination, laboratory investigations (including complete blood cell count with differential, alanine aminotransferase, and bilirubin), cranial ultrasonography, and ophthalmologic evaluation. Asymptomatic cases were defined as confirmed cCMV but with no findings on physical examination compatible with disease and normal results for laboratory investigations, neuroimaging, ophthalmology examination, and hearing at birth. Symptomatic disease was defined as one or more abnormalities compatible with cCMV or SNHL at birth. Ninety-six infants with completed assessments (16%) were deemed to have cCMV symptoms and 63 of these (66%) began receiving valganciclovir treatment. Hearing loss was confirmed in 34 of 96 infants (35%; 5.6% of the overall cohort of cCMV cases completing evaluation).

Surprises, Speculations, and Future Directions

Perhaps the biggest surprise described in the report from Dunn and colleagues[15] is the lower than expected rate of detection of cCMV. It seems likely that the DBS PCR currently falls far short of the goal of a test with 100% sensitivity as a screen for cCMV. As noted above, this makes the DBS CMV PCR atypical when compared to other screenable disorders, for which it is considered unacceptable for a screening test to miss even a single case of a given illness, in light of the potentially devastating outcomes that may ensue if one of these disorders goes unrecognized. However, cCMV is different—and that is okay. At this stage, we may be missing cases of cCMV by DBS screening, but we should not let the perfect be the enemy of the good. As Dunn et al[15] report, universal cCMV has been a game changer for many infants in Ontario. The identification of almost 100 symptomatic and more than 500 asymptomatic infants with cCMV for whom anticipatory hearing, speech and language, and neurodevelopmental surveillance can be conducted will improve outcomes for these children.

Future work can determine if other screening approaches for cCMV merit consideration. A report[16] of a high-throughput, pooled saliva screening approach shows promise, although the issue of a false-positive CMV saliva PCR result in any infant who has been breastfed (due to the ubiquitous presence of CMV DNA in the colostrum and breast milk of all seropositive women) is troublesome. Another issue that will need to be resolved is the lack of a uniform case definition of what constitutes symptomatic cCMV disease. This will be important not only in comparing data across different demographic groups, but also in clinical decision-making about which infants might benefit from antiviral therapy. The data from Dunn et al[15] also demonstrate, as has been observed in other universal screening cohorts,[17] the presence of many incidental cranial ultrasound findings, such as subependymal cysts and lenticulostriate vasculopathy. Although these are important issues to resolve, uncertainties about the clinical correlates of such incidental findings are minor concerns when balanced against the good that will be done for Ontario's children by universal cCMV screening. The authors are heartily congratulated for this substantial achievement which will hopefully be the springboard for future US states and Canadian provinces who implement universal cCMV screening into clinical practice.

ARTICLE INFORMATION

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Published Online: January 21, 2025. doi:10.1001/jamapediatrics.2024.5569

Conflict of Interest Disclosures: Dr Schleiss reported grant support but no personal honoraria

from Moderna Vaccines. No other disclosures were reported.

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