Screening for Congenital Cytomegalovirus After Newborn Hearing Screening: What Comes Next?

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Congenital cytomegalovirus (cCMV) infection is a common and yet underappreciated cause of hearing loss and neurodevelopment disability in US children.[1] Any opportunity to achieve early detection of cCMV and provide interventions warrants careful consideration.

Diener et al[2] in this issue document the experience with targeted screening for cCMV in Utah among infants who do not pass newborn hearing screening (NBHS). Since July 2013, Utah has required referral for testing for cytomegalovirus (CMV) within 21 days of birth for newborns who do not pass NBHS and follow-up outpatient screening.[3] Most notably, the introduction of targeted screening for cCMV, along with state-funded public education about cCMV, was associated with an increase from 56% to 77% in timely diagnostic audiology follow-up (<90 days) of infants who did not pass NBHS.[2] That is important because timely diagnosis and early intervention for sensorineural hearing loss (SNHL) improves long-term language outcomes.[4]

That said, Utah's experience with targeted screening (ie, targeted testing based on a marker of suspected infection[5]) raises as many questions as it answers. Targeted screening for cCMV resulted in the identification of 14 children with confirmed cCMV in 24 months, but during the same period an estimated 400 to 700 infants in Utah were born with cCMV, based on 103 868 births during that time.[6] If it is indeed urgent to detect infants with cCMV, why not screen all newborns? How do the potential benefits of each approach compare with the costs and burden of testing and follow-up?

Diener et al[2] mention the main benefit of targeted screening as the focused surveillance and monitoring of children with asymptomatic cCMV infections at risk for late-onset and progressive SNHL. However, all infants with cCMV are at risk for SNHL, most of whom are not detected by targeted screening. Furthermore, it is unclear how audiologic monitoring should be done. Although monitoring of children with cCMV for SNHL is endorsed by the Joint Committee on Infant Hearing (2007),[7] it is not stated how often, for how long, or by whom testing should occur.

The other benefit of targeted screening mentioned by Diener et al[2] is the opportunity to diagnose infants with symptomatic cCMV infections, although how this would occur was not explained, and mandated testing in Utah did not detect such infants. Symptomatic cCMV with central nervous system involvement is medically actionable, with treatment with valganciclovir recommended beginning in the first month of life.[8] Two clinical trials of antiviral treatment in such infants demonstrated significantly better hearing and neurodevelopmental outcomes despite the risk of neutropenia.[9,10] Universal screening of newborns for cCMV has the potential of increasing detection of symptomatic infections, but targeted screening

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falls short. In Utah, 13 other infants were clinically diagnosed in 2 years,[2] compared with an expected 40 to 100 symptomatic cases.[11]

A controversial aspect of targeted screening in Utah is that antiviral treatment is offered to asymptomatic infants with cCMV[12] despite a lack of evidence of benefit and safety in that population. That practice is not endorsed by professional societies.[8] Trials of valganciclovir in infants with asymptomatic cCMV are under way, but it will be several years before results are known.[5]

Other questions include how infants should be tested for CMV, how much it costs, and who pays for it. Specimens should be collected within 21 days to test for CMV, which is not easy to do in targeted screening programs if, as in Utah, outpatient NBHS is conducted at ~14 days. The cost of targeted screening in Utah has been reported to be $66 per specimen,[12] but it is unclear what that cost covers. A recent hypothetical cost-effectiveness analysis posited that testing for CMV by using saliva specimens for either targeted or universal screening would cost between $10 and $50 per specimen.[13] However, the analysis assumed no added cost to public health systems, which may be unrealistic.

Universal screening for cCMV would be a substantial undertaking and faces multiple challenges. No prospective population-based pilot screening studies have been conducted to demonstrate feasibility and affordability within a public health context. Use of dried blood spot specimens would be ideal, but sensitivity may be problematic[14,15]; assays using saliva have greater analytic sensitivity but require a new testing infrastructure with associated costs.[16] One study designed to assess high-throughput assays by using both saliva and dried blood spots in screening unselected newborns is under way in Minnesota. Universal newborn cCMV screening would also require standardized protocols and data systems for monitoring large numbers of children with cCMV, along with assessment of workforce capacity. Finally, consensus is needed on which infants with cCMV are appropriate candidates for medical treatment.

The experience of Utah as the first state to implement targeted screening for cCMV is instructive and will contribute to discussions of appropriate ways to achieve early detection of cCMV and provide suitable services for affected children.

ABBREVIATIONS

CMV: cytomegalovirus
cCMV: congenital cytomegalovirus
NBHS: newborn hearing screening
SNHL: sensorineural hearing loss

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