Neuroimaging Results from a Universal Congenial CMV (cCMV) Screening Study in Minnesota

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Congenital Cytomegalovirus Infection

- Encompasses a spectrum of symptoms.
- > Most infants are asymptomatic at birth.
- Radiographic abnormalities most consistent with cCMV CNS disease include intracerebral calcifications, periventricular echogenicity, ventriculomegaly, and cortical or cerebellar malformations.







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Congenital cytomegalovirus approved for addition to newborn screening panel

Health News Florida

State would be first to screen all newborns for the infection-caused condition



Minnesota Commissioner of Health Jan Malco has approved an advisory committee's ecommendation to add congenital cytomegalovirus (cCMV) to the list of conditions for which Minnesota whorns are routinely screened paying the way for

Minnesota begins newborn screenings for a common cause of birth defects

Health News Florida | By Michelle Wiley - Minnesota Public Radio f 🎔 in 🖂 Published February 9, 2023 at 11:33 PM EST



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IGHLIGHTING THE VIVIAN ACT AND THE UNIVERSITY OF MINNESOTA'S WORK IN ADVOCATING FOR REGULAR SCREENING

Highlighting the Vivian Act and the University of Minnesota's Work in Advocating for Regular Screening

Because of the Vivian Act that was passed, Minnesota is now the first state to start universal screening for congenital Cytomegalovirus (cCMV) in all newborn infants. CMV is a common virus, but the real concern is pregnant mothers passing the virus on to their babies, as this can have more serious health concerns as a result of contracting the disease. Mark Schleiss, MD, Pr KARF the Division of Pediatric Infectious Diseases at the University of Minn began to work with parents whose children were born with cCMV to st ← KARE 11 process of the Vivian Act in 2016. To learn more about this story and th implications of the Vivian act in CMV screening, follow this link.

'Vivian Act' takes aim at underrecognized virus in babies

Minnesota could pioneer screening for congenital cytomegalovirus.

By Editorial Board JULY 15, 2021 - 5:30PM



Seven years ago, the Henrikson fai was minutes away from taking ne Vivian home from the hospital. Tl an astute physician doing a final c on the two-day-old infant called a to the discharge.

"Things just kind of aren't adding up," Leah Henrikson remembers him saying. Leading up to that, Vivian had a constellation of symptoms - some

Minnesota becomes first state to screen newborns for CMV

Minnesota health professionals and parents are celebrating a milestone in health screening.



It is imperative to define the optimal neuroimaging for cases.

In February 2023, Minnesota's universal cCMV

screening bill went into effect.

Cranial ultrasound (US) is a safe, non-invasive technique to examine neonatal brains, advocated for by an international panel for cCMV disease classification (PMID: 28291720).





Objectives

Determine the clinical manifestations of cCMV in infants identified in the context of a universal screening study. Characterize cranial US, CT, and MRI findings observed during the diagnostic evaluation of confirmed cCMV cases.



Methods

- 5 well-baby newborn nurseries and 3 neonatal intensive care units.
- PCR was performed on dried blood spots and saliva swabs. Screen-positive infants had a confirmatory urine PCR test within 21 days of birth.
- Infants with positive screens obtained follow-up and characterized using Rawlinson et al. criteria (PMID: 28291720).
- Clinical evaluation included cranial US to evaluate for central nervous system pathology, MRI and CT as indicated.



Panel 2: Definitions of congenital cytomegalovirus infection and disease

Moderately to severely symptomatic congenital cytomegalovirus disease

- Multiple manifestations attributable to congenital cytomegalovirus infection: thrombocytopenia, petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, hepatitis (raised transaminases or bilirubin), or
- Central nervous system involvement such as microcephaly, radiographic abnormalities consistent with cytomegalovirus central nervous system disease (ventriculomegaly, intracerebral calcifications, periventricular echogenicity, cortical or cerebellar malformations), abnormal cerebrospinal fluid indices for age, chorioretinitis, sensorineural hearing loss, or the detection of cytomegalovirus DNA in cerebrospinal fluid

Mildly symptomatic congenital cytomegalovirus disease

 Might occur with one or two isolated manifestations of congenital cytomegalovirus infection that are mild and transient (eg, mild hepatomegaly or a single measurement of low platelet count or raised levels of alanine aminotransferase). These might overlap with more severe manifestations. However, the difference is that they occur in isolation

Asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss

• No apparent abnormalities to suggest congenital cytomegalovirus disease, but sensorineural hearing loss (≥21 decibels)

Asymptomatic congenital cytomegalovirus infection

• No apparent abnormalities to suggest congenital cytomegalovirus disease, and normal hearing

Definitions as published by Kimberlin and colleagues,⁶ with minor emendation from discussions of the International Congenital Cytomegalovirus Recommendations Group

- Confirmatory urine PCR <21 days
- CBC, LFT, serology, blood viral load
- Audiology, ophthalmology
- Cranial US
- Long-term neurodevelopmental follow-up
- Disease category
 classification

Lancet Infect Dis 2017; 17: e177-88

Neuroimaging Options: Cranial Ultrasound

- Ultrasound (high-frequency sound wave) imaging of the brain through the fontanelles of the skull.
- > An imaging technique unique to infants.
- > Evaluates for anatomical variations, bleeding, and hydrocephalus.
- > Widely used in neonatal intensive care units.

Advantages

Disadvantages

- Safe, non-invasive, readily available, and reproducible.
- Portable, baby friendly (can be done at the bed side with little disturbance to the baby), inexpensive.
- Does not require ionizing radiation or sedation. Can be repeated as necessary, making it suitable for serial imaging to assess the growth and maturation of the brain.

- Operator-dependent, so requires specialized training for ultrasound personnel.
- Image quality also depends on the acoustic windows used and the presence of hair.
- Structures that comprise the acoustic windows eventually close, so it can only be used for a certain age range of patients.

Anatomy on Cranial Ultrasound





Neuroimaging Options:

Computerized tomography

- Combines a series of X-ray images taken from different angles then creates cross-sectional images (slices).
- > Can be performed with or without contrast depending on indication.
- Provides additional information when compared to cranial ultrasound to define brain lesions, establish diagnosis, guide treatment decisions.

Advantages

Disadvantages

Time-efficient, good for use during emergencies. Less need for sedation due to the faster nature.

Less costly than MRI.

Provides more detailed imaging than ultrasound, but in general less detailed than MRI. Exposure to ionizing radiation, generally best avoided during childhood when possible.

Although less expensive than MRI, still may be difficult to implement on a large scale.

Neuroimaging Options:

Magnetic resonance imaging

- Strong magnetic field created by the MRI scanner causes the atoms in body to align in the same direction, which is used to generate the image.
- MRI provides the most detailed information about an atomical structures and variations in the brain.
- Different types of sequences (e.g. T1, T2, FLAIR, DWI) provide ideal informatio about different body tissue types.

Advantages

Disadvantages

- Provides the most detailed anatomical information.
- Many hospitals now have quick brain MRI protocols and feed/swaddle technique can reduce the need for sedation in infants.
- Does not require ionizing radiation.

- Most expensive option; cost may be prohibitive when implementing on a larger scale.
- Children may require sedation to remain still enough to obtain images, this may prolong hospital stay.
- Quick brain protocols do not have as much fine detail.



68 (78%) infants asymptomatic and 19 (22%) had signs or sequelae of cCMV



What Did Cranial Ultrasounds Reveal?

Cranial Ultrasound Result	Number of Infants
Normal	53
Cystic lesions (subependymal	10 ^{<i>f</i>}
cysts; choroid plexus cysts)	
Mineralizing vasculopathy	6
Intracranial calcifications	5*†
Subependymal hemorrhages	1
Caudothalamic groove	1
heterogeneity	
TOTAL	76



^fThree infants in this group also had mineralizing vasculopathy.

*cCMV-defining abnormality for assignment to "CMV disease" category.

[†]One infant in this group also had mineralizing vasculopathy, one other infant in this group also had cystic lesions.







	Symptomatic or Asymptomatic with SNHL	Asymptomatic
Incidental Abnormal Ultrasound Results	9	9
Normal Ultrasound Results	4	49

Imaging Examples



Discussion

Cases of cCMV should be considered within an entire context of developmental testing, clinical examination, and laboratory workup.

- Consider MRI if concerns arise during the comprehensive assessment of the child.
- Some brain changes can be very difficult to see on head ultrasound but much clearer on MRI. In these kind of cases when there is some other concern, even mild/subtle, it should be strongly considered to obtain a brain MRI, even if the head ultrasound is "normal" or "nonspecific".

Conclusions

- PCR of newborn DBS and/or saliva revealed a prevalence of
 3.7 per 1000 in a universal cCMV screening study.
- Most infants had normal cranial US, and most cUS abnormalities were not pathognomonic for cCMV disease.
 Incidental cUS findings were common. Only 5/76 had a typical cCMV-defining abnormality.
- Clarification is needed regarding which cUS findings require detailed follow-up, including CT and MRI, as universal cCMV screening moves forward in clinical practice.



References

- 1. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17(4):253-76.
- 2. Gabrielli L, Bonasoni MP, Santini D, Piccirilli G, Chiereghin A, Petrisli E, Dolcetti R, Guerra B, Piccioli M, Lanari M, Landini MP, Lazzarotto T. Congenital cytomegalovirus infection: patterns of fetal brain damage. Clin Microbiol Infect 2012;18(10):E419-27. doi: 10.1111/j.1469-0691.2012.03983.x. PMID: 22882294.
- 3. Ronchi A, Zeray F, Lee LE, et al. Evaluation of clinically asymptomatic high risk infants with congenital cytomegalovirus infection. J Perinatol 2020;40(1):89-96. doi:10.1038/s41372-019-0501-z.
- 4. Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, Daly K, Doutré S, Gibson L, Giles ML, Greenlee J, Hamilton ST, Harrison GJ, Hui L, Jones CA, Palasanthiran P, Schleiss MR, Shand AW, van Zuylen WJ. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis* 2017;17(6):e177-e188. doi: 10.1016/S1473-3099(17)30143-3. PMID: 28291720.
- 5. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007; 17(5):355-363. doi:10.1002/rmv.544.
- 6. Bartlett AW, McMullan B, Rawlinson WD, Palasanthiran P. Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: A systematic review. Rev Med Virol 2017;27:e1938. doi: 10.1002/rmv.1938.
- 7. Smithers-Sheedy H, Raynes-Greenow C, Badawi N, Reid SM, Meehan E, Gibson CS, Dale RC, Jones CA. Neuroimaging findings in a series of children with cerebral palsy and congenital cytomegalovirus infection. Infect Disord Drug Targets 2014;14(3):185-90. doi: 10.2174/1871526515999150320154858. PMID: 25809629.
- 8. Zhou YP, Mei MJ, Wang XZ, et al. A congenital CMV infection model for follow-up studies of neurodevelopmental disorders, neuroimaging abnormalities, and treatment. JCI Insight 2022;7(1):e152551. doi:10.1172/jci.insight.152551.
- 9. Gabrielli L, Bonasoni MP, Santini D, Piccirilli G, Chiereghin A, Petrisli E, Dolcetti R, Guerra B, Piccioli M, Lanari M, Landini MP, Lazzarotto T. Congenital cytomegalovirus infection: patterns of fetal brain damage. Clin Microbiol Infect 2012;18(10):E419-27. doi: 10.1111/j.1469-0691.2012.03983.x. PMID: 22882294.
- 10. Lucignani G, Guarnera A, Rossi-Espagnet MC, Moltoni G, Antonelli A, Figà Talamanca L, Carducci C, Calo Carducci Fl, Napolitano A, Gandolfo C, Campi F, Auriti C, Parazzini C, Longo D. From Fetal to Neonatal Neuroimaging in TORCH Infections: A Pictorial Review. Children 2022; 9(8):1210. https://doi.org/10.3390/children9081210.
- 11. Lanari M, Capretti MG, Lazzarotto T, Gabrielli L, Rizzollo S, Mostert M, Manzoni P. Neuroimaging in CMV congenital infected neonates: how and when. Early Hum Dev 2012;88 Suppl 2:S3-5. doi: 10.1016/S0378-3782(12)70003-8. PMID: 22633509.
- 12. Leung J, Dollard SC, Grosse SD, Chung W, Do T, Patel M, Lanzieri TM. Valganciclovir Use Among Commercially and Medicaid-insured Infants With Congenital CMV Infection in the United States, 2009-2015. Clin Ther. 2018 Mar;40(3):430-439.e1. doi: 10.1016/j.clinthera.2018.01.006. Epub 2018 Feb 4. PMID: 29397198; PMCID: PMC5857424.
- 13. Counsell SJ, Arichi T, Arulkumaran S, Rutherford MA. Chapter 4 Fetal and neonatal neuroimaging, Editor(s): Linda S. de Vries, Hannah C. Glass, Handbook of Clinical Neurology, Elsevier, Volume 162, 2019, Pages 67-103, ISSN 0072-9752, ISBN 9780444640291, https://doi.org/10.1016/B978-0-444-64029-1.00004-7.
- 14. Dollard SC, Dreon M, Hernandez-Alvarado N, Amin MM, Wong P, Lanzieri TM, Osterholm EA, Sidebottom A, Rosendahl S, McCann MT, Schleiss MR. Sensitivity of Dried Blood Spot Testing for Detection of Congenital Cytomegalovirus Infection. JAMA Pediatr 2021;175(3):e205441. doi: 10.1001/jamapediatrics.2020.5441.

References

- Schleiss MR, Rosendahl S, McCann M, Dollard SC, Lanzieri TM. Assessment of Congenital Cytomegalovirus Prevalence Among Newborns in Minnesota During the COVID-19 Pandemic. JAMA Netw Open 2022;5(9):e2230020. doi: 10.1001/jamanetworkopen.2022.30020.
- 2. Gustavo Malinger, Edgardo Corral Sereño, Tally Lerman-Sagie, The Differential Diagnosis of Fetal Intracranial Cystic Lesions, Ultrasound Clinics, Volume 3, Issue 4, 2008, Pages 553-558,
- 3. Hoki C, White M, Pesch MH, Melvin AJ, Park AH. A Cross-Sectional Survey of Pediatric Infectious Disease Physicians' Approach to Congenital Cytomegalovirus Infection. Int J Neonatal Screen 2023;9(2):17. doi: 10.3390/ijns9020017.
- 4. Fink KR, Thapa MM, Ishak GE, Pruthi S. Neuroimaging of pediatric central nervous system cytomegalovirus infection. Radiographics 2010;30(7):1779-96. doi: 10.1148/rg.307105043. PMID: 21057120.
- 5. Giannattasio A, Di Costanzo P, Milite P, De Martino D, Capone E, Romano A, Bravaccio C, Capasso L, Raimondi F. Is lenticulostriated vasculopathy an unfavorable prognostic finding in infants with congenital cytomegalovirus infection? J Clin Virol 2017;91:31-35. doi: 10.1016/j.jcv.2017.04.006.
- 6. Amir J, Schwarz M, Levy I, Haimi-Cohen Y, Pardo J. Is lenticulostriated vasculopathy a sign of central nervous system insult in infants with congenital CMV infection? Arch Dis Child 2011;96(9):846-50. doi: 10.1136/adc.2010.208405.
- 7. Bilavsky E, Schwarz M, Pardo J, Attias J, Levy I, Haimi-Cohen Y, Amir J. Lenticulostriated vasculopathy is a high-risk marker for hearing loss in congenital cytomegalovirus infections. Acta Paediatr 2015;104(9):e388-94. doi: 10.1111/apa.13053.
- 8. Smiljkovic, M., Renaud, C., Tapiero, B. et al. Head ultrasound, CT or MRI? The choice of neuroimaging in the assessment of infants with congenital cytomegalovirus infection. BMC Pediatr 19, 180 (2019). https://doi.org/10.1186/s12887-019-1562-z
- 9. Capretti MG, Lanari M, Tani G, Ancora G, Sciutti R, Marsico C, Lazzarotto T, Gabrielli L, Guerra B, Corvaglia L, Faldella G. Role of cerebral ultrasound and magnetic resonance imaging in newborns with congenital cytomegalovirus infection. Brain Dev 2014;36(3):203-11. doi: 10.1016/j.braindev.2013.04.001. PMID: 23647916.
- 10. Keymeulen A, De Leenheer E, Casaer A, Cossey V, Herregods N, Laroche S, Mahieu L, Van Mol C, Vanhaesebrouck S, Walle CV, Smets K. Cranial ultrasound and MRI: complementary or not in the diagnostic assessment of children with congenital CMV infection? *Eur J* Pediatr 2022;181(3):911-920. doi: 10.1007/s00431-021-04273-y. PMID: 34636957.
- 11. http://www.imagegently.org/About-Us/Campaign-Overview#:~:text=The%20Campaign%20Overview,member%20of%20the%20care%20team.

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