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CMV and Hearing Loss

Nathan Page, MD, FAAP -
Phoenix Children's Hospital

Aditi Bhuskute, MD, FAAP -
University of California, Davis

Nathan Page, MD

Dr. Page is the director of the cochlear implant team at Phoenix Children's Hospital and the EHDI Chapter Champion for the Arizona chapter of the AAP. He is a founding member of StopCMVAZ and is actively involved in efforts to improve education and understanding of CMV in Arizona.

Aditi Bhuskute, MD

Dr. Bhuskute is a fellowship trained pediatric otolaryngologist and practices in the full range of pediatric ear, nose and throat disorders at UC Davis Medical Center. She has special interests in hearing loss, cochlear implantation, chronic ear disease, and aerodigestive disorders. She is interested in quality improvement and resident education, and strongly supports multidisciplinary care for children.

What is CMV?

Cytomegalovirus
(sy·toe·MEG·a·low·vy·rus)

- Common virus that is usually harmless to healthy kids and adults but can cause cold-like symptoms (sore throat, fever, fatigue and swollen glands)
- Most adults have been infected with CMV by the time they are 40 years old
- Common in children ages 1-3 years old, especially if they attend day care
- Herpesvirus: Once you are infected, CMV stays in your body in an inactive (latent) state that reactivates (lytic state) throughout your life.

You or your child can have a hidden infection with no signs or symptoms (asymptomatic)

Kathleen M. Muldoon, PhD
College of Graduate Studies
Arizona College of Osteopathic Medicine
Midwestern University

Scientific Advisory Committee, Chair
National CMV Foundation

Congenital CMV is preventable.

CMV can survive on objects,

such as hands, faces, toys, pacifiers, teething rings, food, plates, cups, straws, forks, spoons, and knives

long enough to be transmitted between people by touching surfaces.

Taking these actions while pregnant will protect your baby from ALL germs:

Wash hands often with soap & water, especially after changing diapers, wiping faces, or touching objects that have been drooled on.

Give hugs & kisses on the **forehead or top of head** to avoid drool.

Clean and disinfect surfaces & objects, such as toys, often.

Eat only your **own** food & drink.

Use only your **own** cup, plate, straws, forks, spoons & knives.

Use only your **own** toothbrush.

STOP CMV AZ

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College of Graduate Studies
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Midwestern University

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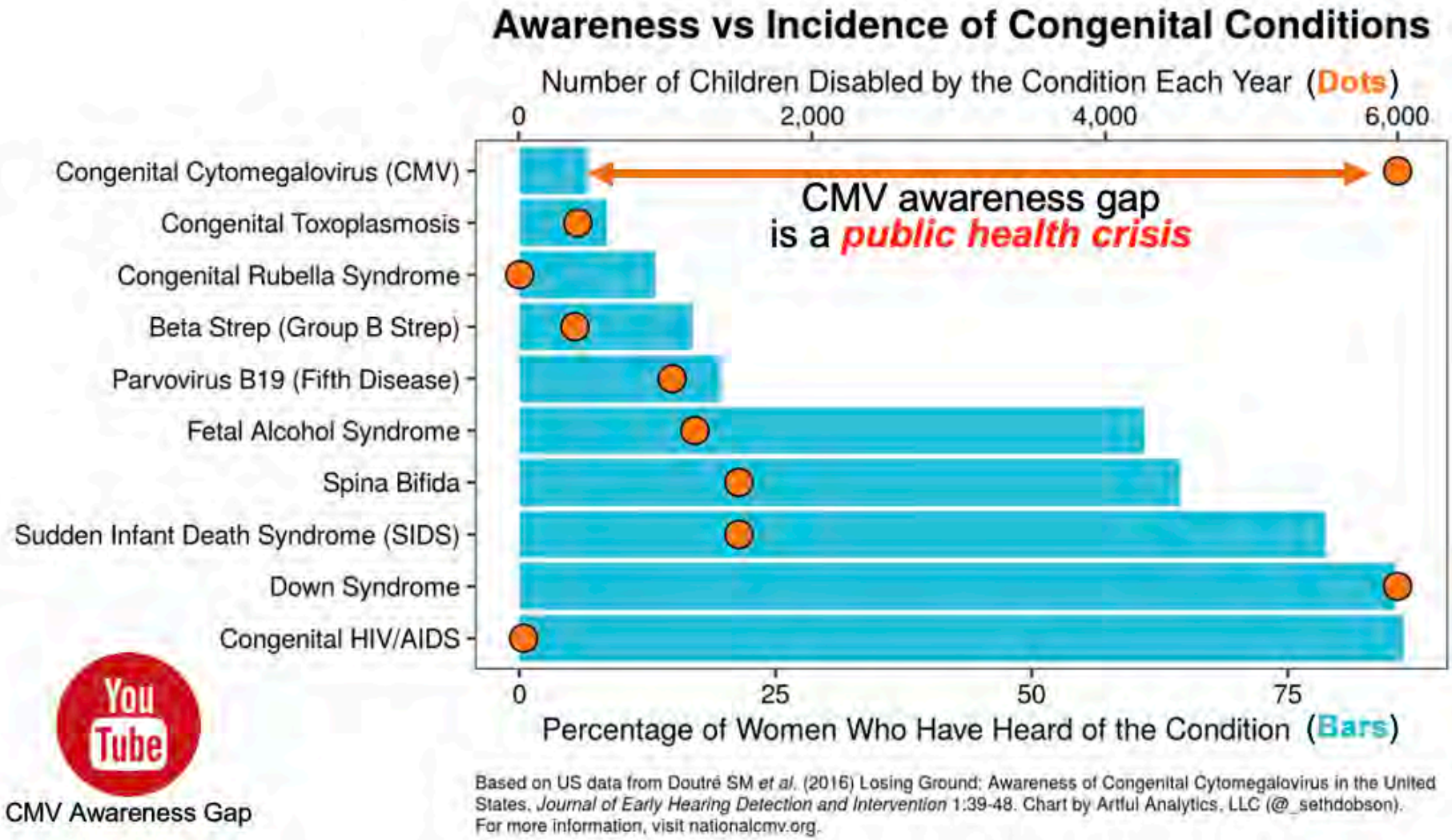
National CMV Foundation



Based on US data from Doutré SM *et al.* (2016) Losing Ground: Awareness of Congenital Cytomegalovirus in the United States, *Journal of Early Hearing Detection and Intervention* 1:39-48. Chart by Artful Analytics, LLC (@_sethdobson). For more information, visit nationalcmv.org.

CMV Awareness Gap

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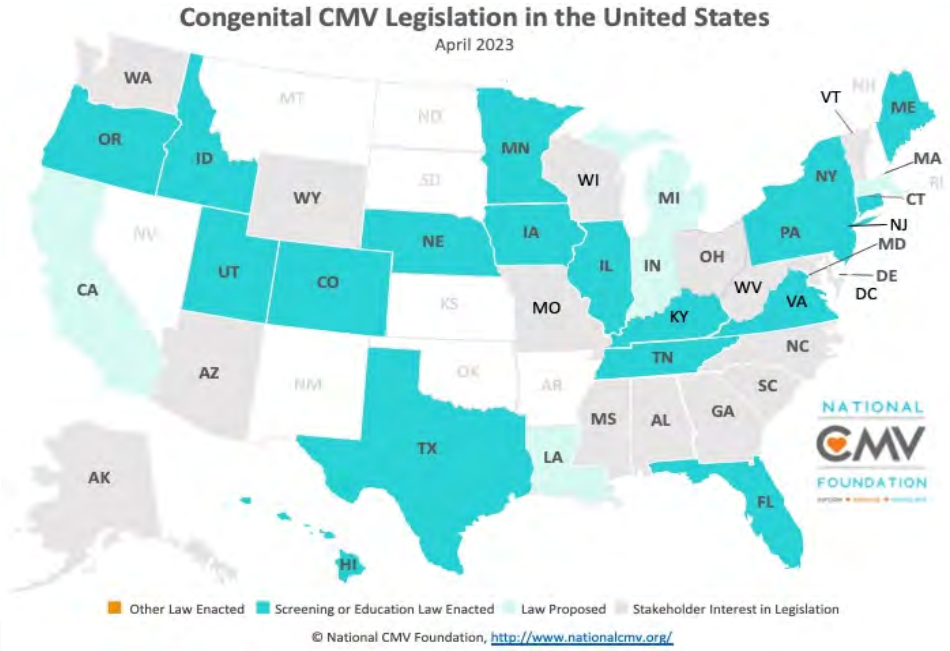
National CMV Foundation

Screening

- Universal CMV screening is not currently standard of care in the US
- State by state organization
- In 2013, Utah became the first state to implement Hearing targeted screening
- In 2023, Minnesota became the first state to implement universal screening



Screening

Universal	Hearing Targeted	Expanded Targeted

• Every child tested
• ID every case
• $$$
	• Screening based on newborn hearing screen results
	• Decreased cost and scope of screening
	• May improve diagnostic outcomes for all infants who fail NBHS
	• No diagnosis for cCMV cases without hearing loss
	• 43% of infants with cCMV related hearing loss will be missed
		• Screening for any infant meeting criteria:
		  • Failed hearing screen
		  • Maternal +CMV
		  • Elevated liver labs
		  • Abnormal CNS imaging
		  • Thrombocytopenia
		  • IUGR
		  • SGA
		  • Macro/microcephaly
		  • Intra-abdominal calcifications
		  • Hepatosplenomegaly
		  • Petechiae

cCMV Screening Methods

- Saliva
- Urine
- Blood (dried blood spot)

- Obtained prior to 3 weeks of age

Testing after 3 weeks?

104 infants who had failed NBHS in at least one ear:

- CMV PCR
- PCR Titers
- Cultures

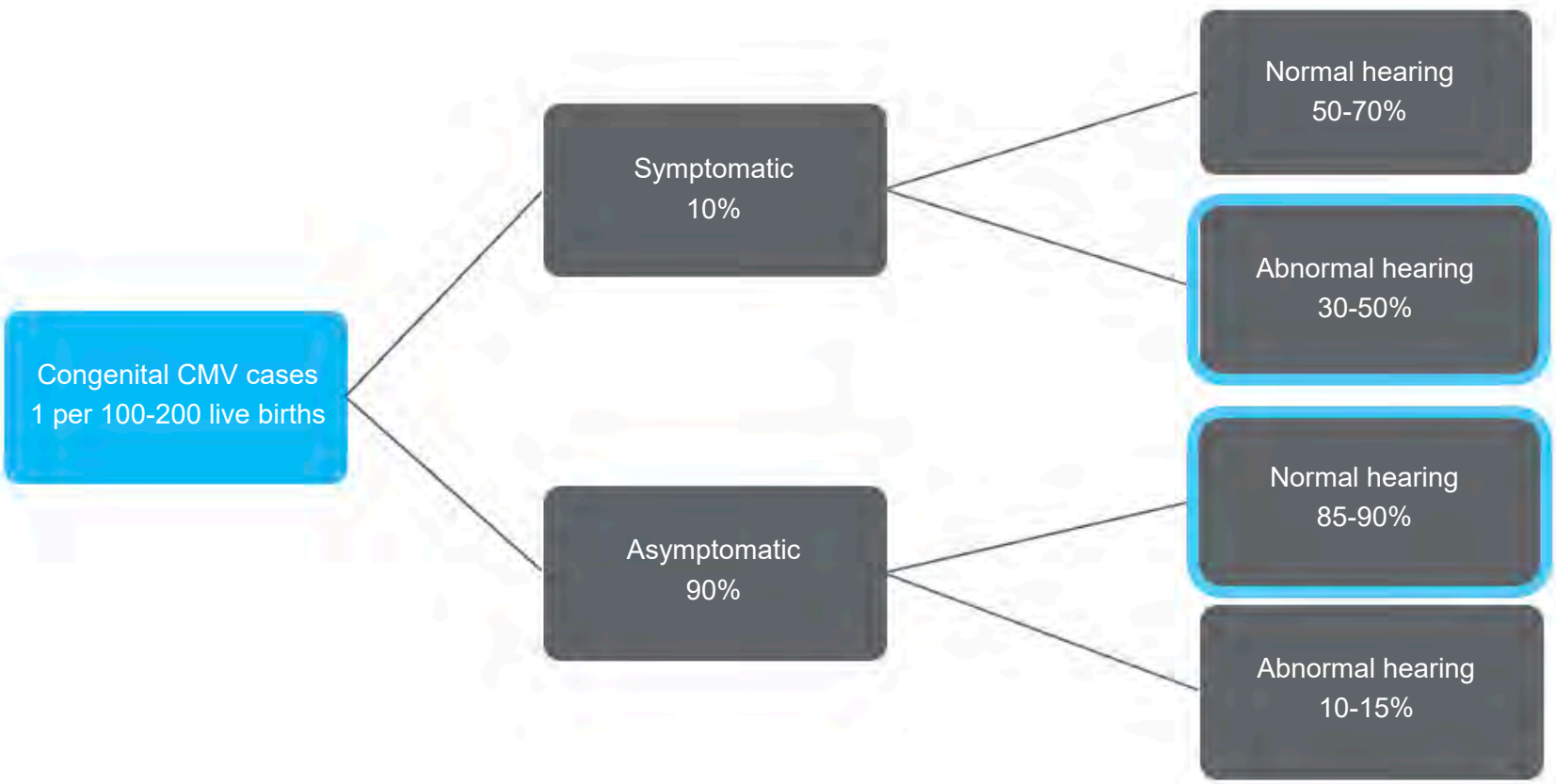
Group 1 – cCMV-associated SNHL	Group 2 – SNHL from other etiologies
Group 3 – Does not fit Groups 1 or 2	Group 4 – Age-matched, normal hearing controls

Lee, Sang-Yeon, Heong Won Jeon, So-Yeon Ahn, Seung-Ha Oh, Bong Jik Kim, and Byung Yoon Choi. "Significance of Cytomegalovirus Tests after Three Weeks of Life in Children with Hearing Loss." International Journal of Pediatric Otorhinolaryngology 168 (2023): 111555. Web.

Testing in Pregnancy

- Traditional testing strategy:
  - IgM, IgG
    - 84.6% conclusive results
    - 15.4% needed follow up testing
  - Anti p52 CMV IgM and anti-gB CMV IgG ELISA
    - 92.8% conclusive results
    - 7.2% needed follow up testing

Warnecke J, et al. Efficiency of CMV serodiagnosis during pregnancy in daily laboratory routine. Journal of Virological Methods 314 (2023) 114685.


Congenital CMV cases
1 per 100-200 live births
Symptomatic
10%
Asymptomatic
90%
Normal hearing
50-70%
Abnormal hearing
30-50%
Normal hearing
85-90%
Abnormal hearing
10-15%

Antiviral Treatment

- Consensus guidelines suggest therapy should not routinely be recommended for children with congenital CMV with isolated SNHL

Rawlinson WD et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis. 2017; 17:e177-e88.

Can early treatment change hearing outcomes?

Symptomatic Patients

Short Term

- Collaborative Antiviral Study Group
- Six month course of valganciclovir provides a modest improvement in hearing and neurocognitive outcomes (Kimberlin)
  - More stable hearing than those infants who received no treatment
  - Those who did not receive treatment had hearing deterioration at 6 months (41% of untreated vs none of the treated individuals)
  - At one year, untreated group had 68% of infants with hearing deterioration, treated group at 21%

Long Term

- McCrary et al demonstrated almost all patients (small same size of 16 participants) with symptomatic cCMV had worsening of their hearing over the course of two years

Kimberlin DW et al. Valganciclovir for symptomatic congenital cytomegalovirus disease, N. Engl. J. Med 372 (2015) 933-943
McCrary H et al. Long-Term Hearing Outcomes of Children with Symptomatic Congenital CMV Treated with Valganciclovir. Int J Pediatr Otorhinolaryngol. 2019 March; 118:124-127

Asymptomatic Patients

- Retrospective studies of children with isolated SNHL who had antiviral therapy showed improvement in hearing loss over the course of one year (Pasternak)
- Observational study of children with isolated SNHL who had antiviral therapy showed improvement in hearing loss over the course of one year
  - 69% of ears improved (53/55 returned to normal)
  - 76% of Children with bilateral HL improved (15/16 normal)

Pasternak, et al. Valganciclovir Is Beneficial in Children with Congenital Cytomegalovirus and Isolated Hearing Loss. J Pediatr. 2018 Aug; 199: 166-170

- Lackner et al identified 23 children with asymptomatic cCMV infection and 12 were treated, 11 were observed. Observation period 4-10 years.
  - One year- 23 children with normal hearing
  - 4 children lost to follow up
  - 18 children observed, only two had hearing loss (both untreated at birth)

Lackner et al. J Laryngol Otol. 2009 April

Pathophysiology: Possible Mechanisms

- Loss of spiral ganglion neurons
- Immune-mediated injury in response to the virus
- Direct cellular injury from the virus itself

Asymptomatic Patients

Currently there is a phase 2 clinical trial utilizing valganciclovir in the treatment of asymptomatic congenital CMV infection

Primary objective

- Estimate the proportion of subjects with asymptomatic cCMV who develop SNHL by 6 months after 4 months of antiviral therapy

Secondary objectives

- Define the safety of valganciclovir therapy
- Estimate the proportion of subjects with asymptomatic cCMV who develop SNHL by 18 months of life after 4 months of antiviral therapy

Randomized Controlled Trial of Valganciclovir for Cytomegalovirus Infected Hearing Impaired Infants: ValEAR Trial

Determine the clinical benefit and safety of antiviral therapy for asymptomatic congenital cytomegalovirus (cCMV) infected hearing-impaired infants.

We will conduct a multi-center double-blind randomized placebo-controlled trial to determine whether hearing-impaired infants with asymptomatic cCMV have better hearing and language outcomes if they receive valganciclovir antiviral treatment.

We will also determine the safety of antiviral valganciclovir therapy for asymptomatic cCMV-infected hearing impaired infants.

- Primary objective
  - To determine if treatment of cCMV-infected hearing impaired infants with isolated hearing loss with the antiviral drug valganciclovir reduces the mean slope of total hearing thresholds over the 20 months after randomization compared to untreated cCMV-infected infants with isolated hearing loss.

- Secondary objectives
  - To determine if valganciclovir treatment improves the following outcomes when compared to the control group:
    - The slope of best ear hearing thresholds over the 20 months after randomization.
    - The MacArthur-Bates Communicative Development Inventory (CDI) percentile score for words produced at 20 months of age.

Natural History of HL in cCMV

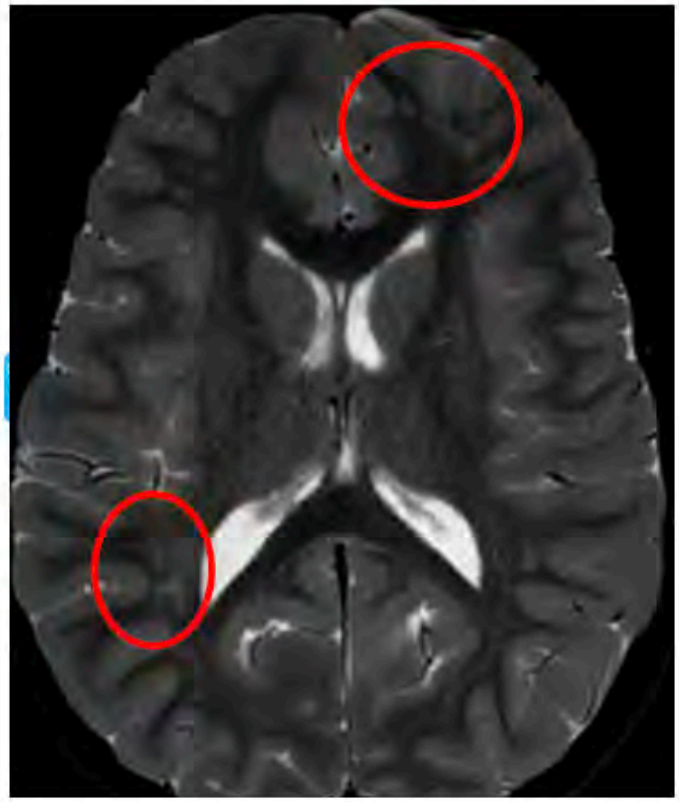
- Most commonly present at birth (80-90%)
- Late onset in 10-20%
- Frequently unilateral
- Frequently progressive

Hearing Trajectory

Symptomatic – 51% of ears congenital SNHL
17% delayed onset

Asymptomatic – 5% congenital SNHL
11% delayed onset

Patients with white matter lesions on MRI – 4x more likely to have delayed onset SNHL by 5yo



Lanzieri TM, Chung W, Leung J, Caviness AC, Baumgardner JL, Blum P, Bialek SR, Demmler-Harrison G; Congenital Cytomegalovirus Longitudinal Study Group. Hearing Trajectory in Children with Congenital Cytomegalovirus Infection. Otolaryngol Head Neck Surg. 2018 Apr;158(4):736-744. doi: 10.1177/0194599818758247. Epub 2018 Mar 20. PMID: 29557247; PMCID: PMC5880689.

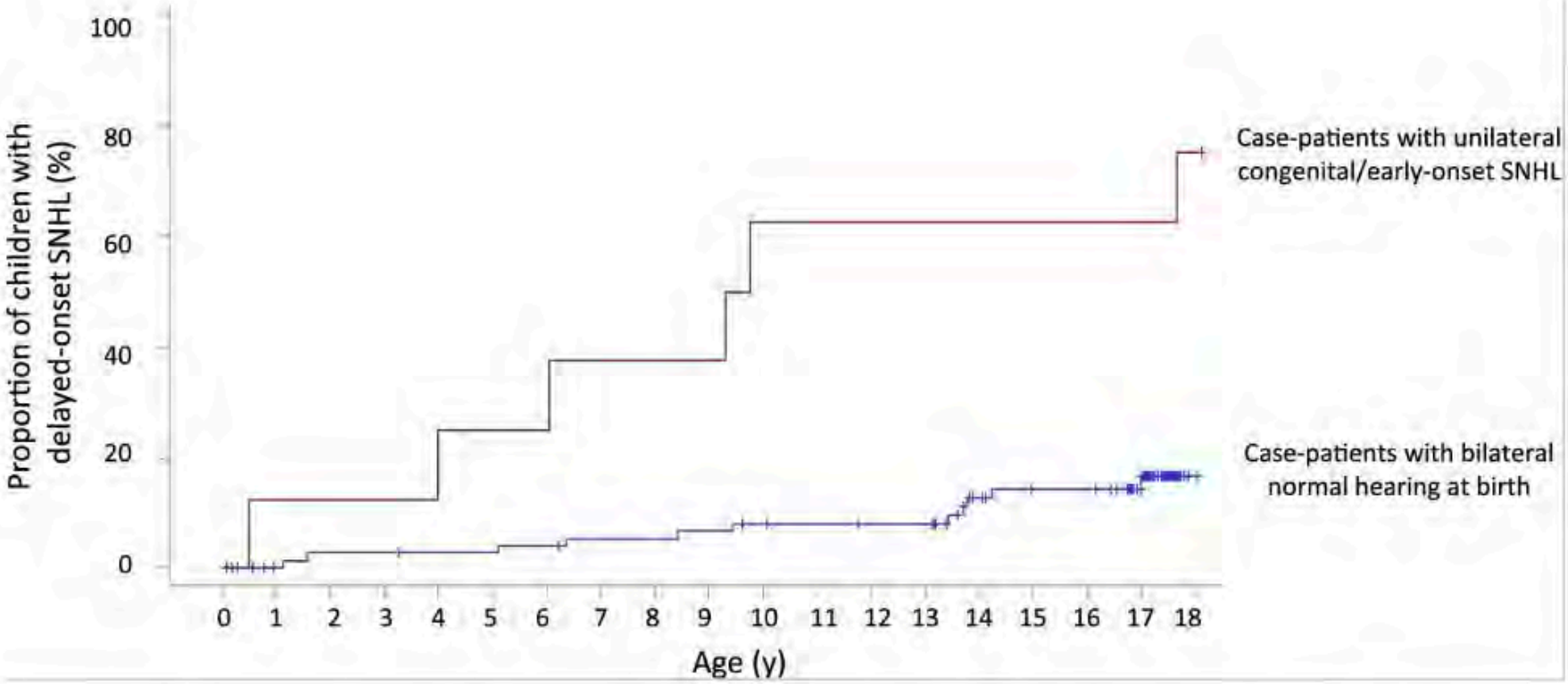
Unilateral hearing loss

- 12.5% had decline in better hearing ear during 4.5 years mean follow up
- 70% had decline in impaired ear

- For patients with congenital UHL
  - 75% developed hearing loss in the normal hearing ear

Tissera KA, Williams A, Perry J, Kawai K, Kenna M, Mankarious LA. Hearing Stability in Patients With Unilateral Hearing Loss Due to Congenital CMV. Otolaryngol Head Neck Surg. 2022 Feb 8:1945998221076439. doi: 10.1177/01945998221076439. Epub ahead of print. PMID: 35133894.

Lanzieri T, et al. Hearing trajectory in children with congenital cytomegalovirus infection. Otolaryngol Head Neck Surg. 2018 April ; 158(4): 736–744. doi:10.1177/0194599818758247.



Significantly greater risk of delayed-onset HL in those with unilateral loss at birth

Lanzieri TM, Chung W, Flores M, Blum P, Caviness AC, Bialek SR, Grosse SD, Miller JA, Demmler-Harrison G; Congenital Cytomegalovirus Longitudinal Study Group. Hearing Loss in Children With Asymptomatic Congenital Cytomegalovirus Infection. Pediatrics. 2017 Mar;139(3):e20162610. doi: 10.1542/peds.2016-2610. Epub 2017 Feb 16. PMID: 28209771; PMCID: PMC5330400.

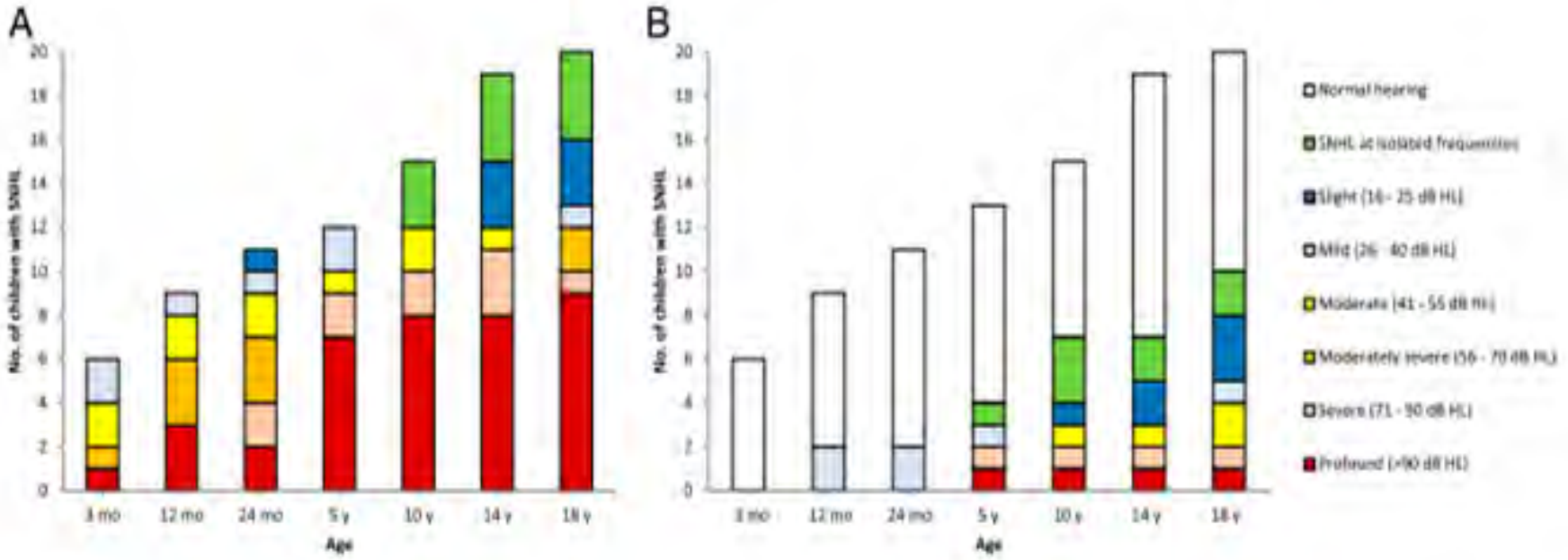


FIGURE 3
Cumulative number of children with asymptomatic congenital CMV infection with SNHL ($n = 20$) by age and SNHL severity in the poorer (A) and better hearing (B) ears.

Congenital SNHL is typically more severe than delayed-onset SNHL

Inner Ear Concerns

- 83/130 children presented with inner ear impairment (64%)
- Risk factors:
  - 1st trimester – Most likely to have hearing loss (OR=4.5)
  - 2nd trimester - Only vestibular impairment
  - 3rd trimester - No cochlear or vestibular impairment

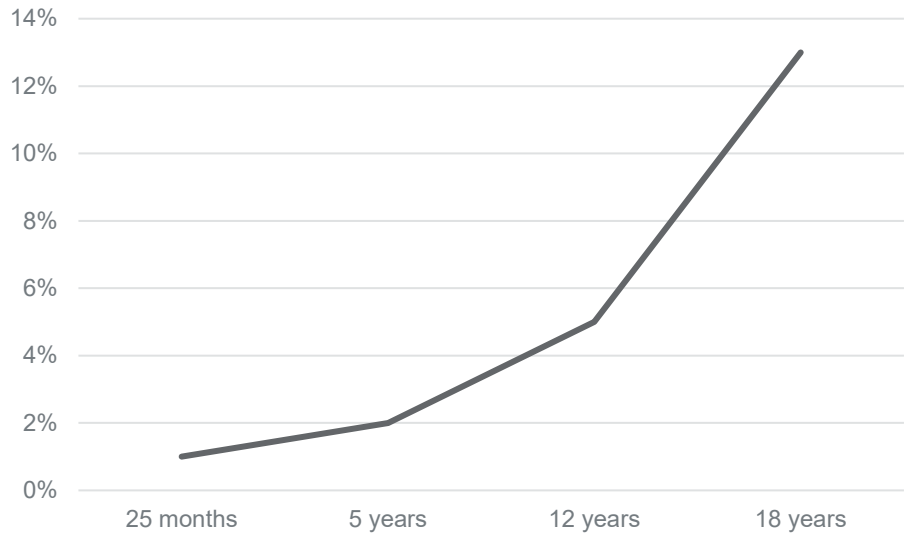
  - Brain lesions on antenatal imaging – much higher risk of inner ear impairment (OR=8.0)

Chebib, et al. Predictors of cochleovestibular dysfunction in children with congenital cytomegalovirus infection. Eur J Pediatr. 2022 May 13. doi: 10.1007/s00431-022-04495-8. Online ahead of print.

Management

- Audiometric surveillance
- Hearing aids/Bone conduction devices
- Cochlear implants

CI Candidacy



Indications for Cochlear Implants

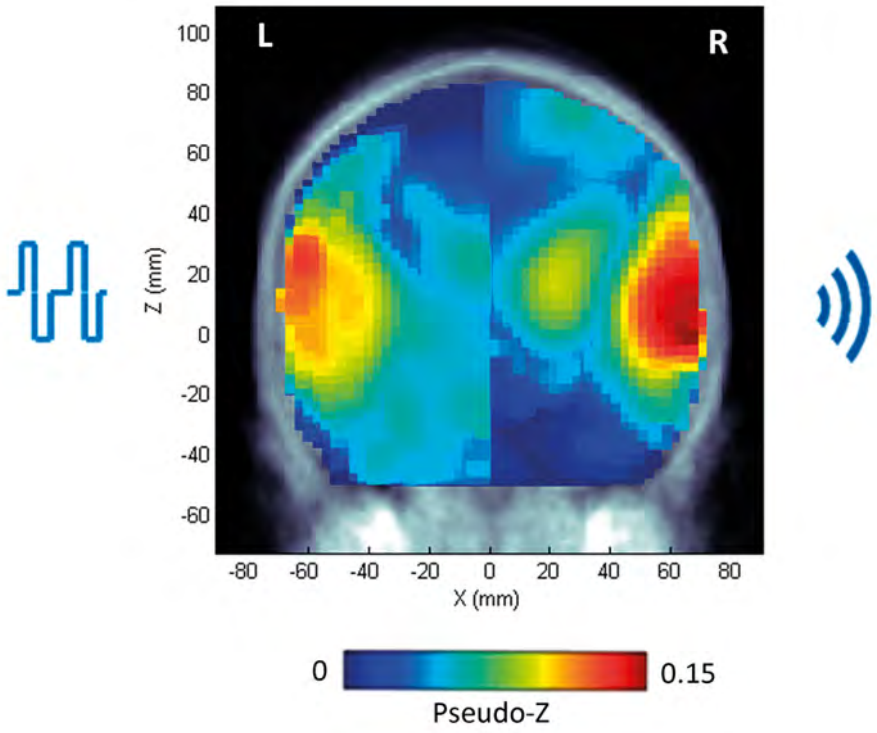
- Bilateral severe to profound sensorineural hearing loss
- Unilateral profound sensorineural hearing loss

Rationale for CI in cCMV UHL

- Common scenario
- Risk of contralateral loss
- Only option to utilize the deaf ear

Outcomes of CI in UHL

- Sound localization improved
- 80% showed meaningful improvement in speech perception in noise and in quiet
- Patients with shorter duration of deafness had better outcomes
- Actually changes the brain



Karen Gordon, Blake Papsin, Sharon Cushing. ENT & AUDIOLOGY NEWS VOLUME 27 ISSUE 5 NOVEMBER/DECEMBER 2018
Benchetrit L, Ronner EA, Anne S, Cohen MS. Cochlear Implantation in Children With Single-Sided Deafness: A Systematic Review and Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2021 Jan 1;147(1):58-69. doi: 10.1001/jamaoto.2020.3852. PMID: 33151295; PMCID: PMC7645748.

Hearing Loss Summary

- Hearing loss in congenital CMV requires long term follow up, at least to age 18.
- Progressive hearing loss is common.
- Antiviral therapy appears to have short-term benefits; long-term benefits are unclear.
- Early identification and treatment of hearing loss is imperative.
- Given the risk of contralateral hearing deterioration in the setting of single sided deafness in cCMV, cochlear implantation should be considered for SSD.
- Screening strategies vary, but all lead to earlier diagnosis, earlier intervention, and likely improved outcomes for children with cCMV

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