



Congenital CMV-Associated Hearing Loss

The hottest topic in OHNS you've never heard about

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OHNS – COVID Talks
 5-6 pm, May 8, 2020

What virus starts with a "C" and doesn't cause global pandemics but is an **urgent, impactful, treatable, common** cause of congenital hearing loss?

Urgent

Requires management within 3 weeks of birth

Impactful

The only non-cancer research study in otolaryngology to have been published in the NEJM in the past 5 years

Treatable

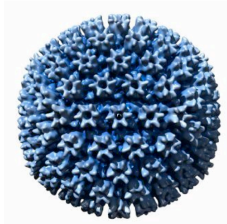
The only medically treatable form of congenital SNHL

Common

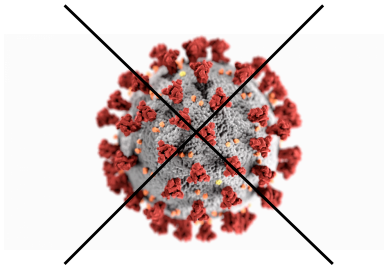
The most common cause of acquired congenital SNHL



CMV Hearing Loss



Cytomegalovirus (CMV)



(NOT coronavirus)

Congenital CMV-associated hearing loss

Characteristics
 Prevalence
 Natural History

CMV Testing

Neonatal testing
 Dried-blood-spot testing

CMV Screening

Universal newborn CMV screening
 Hearing-targeted CMV screening

CMV management

Education, hygiene, and public health
 Antiviral treatment
 Current clinical trials



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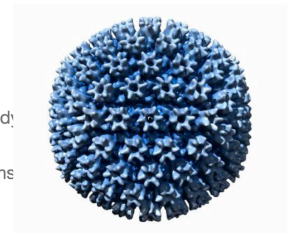
CMV management

Education, hygiene, and public health
 Antiviral treatment
 Current clinical trials



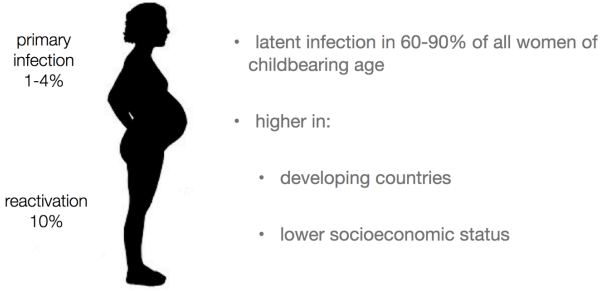
CMV

- Herpesviridae family of DNA viruses
- linear, double-stranded DNA
- infects the majority of cell types in the body
- pathologic features: cytomegaly, inclusions multinucleated giant cells.



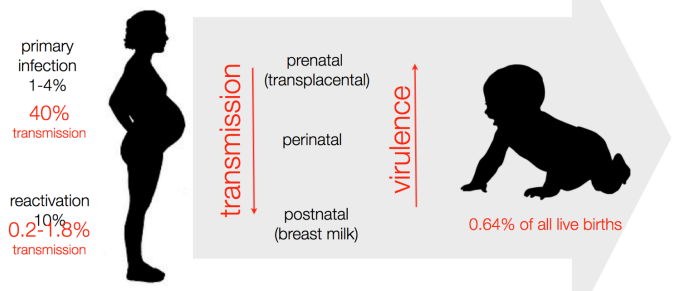
http://terafelox.blogspot.com/2008/06/01_lecture.html

CMV epidemiology



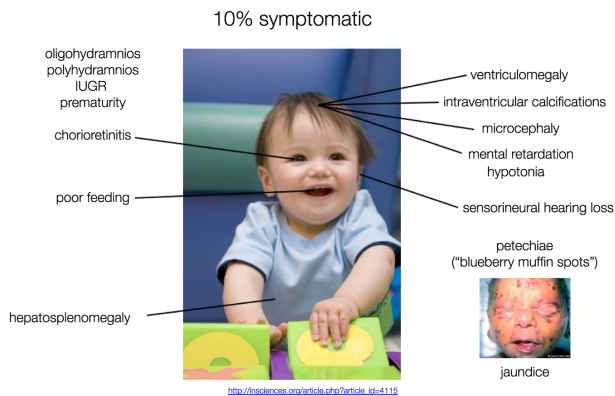
Syggelou, 2010

CMV transmission

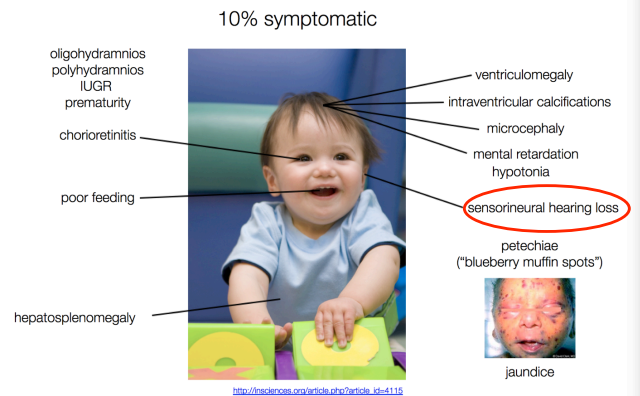


Syggelou, 2010

CMV syndrome

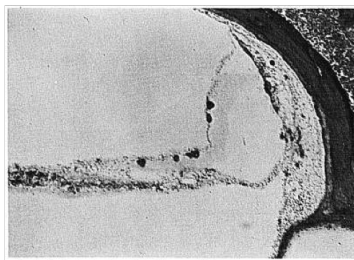


CMV syndrome



CMV Pathophysiology

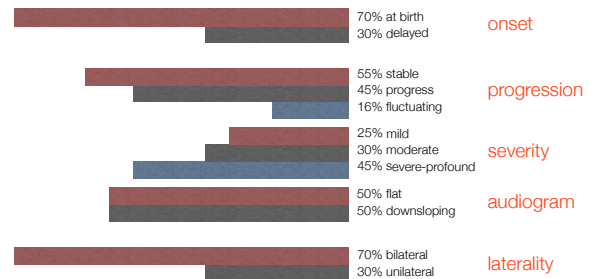
postmortem exam of temporal bone in infant



Myers, 1968

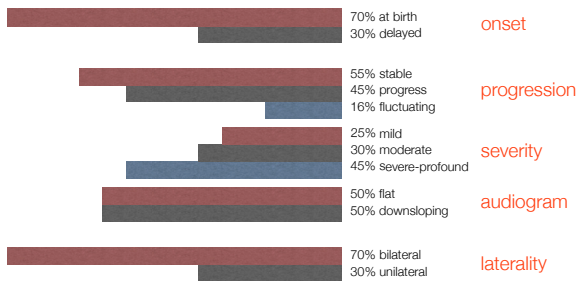
- CMV inclusion bodies found primarily in scala media
- limited number of case studies, may not represent majority of cases
- CMV recovered from perilymph of 4/6 children with CMV-related hearing loss

CMV hearing loss



Williamson, 1992
Rosenthal, 2009
Peters, 2002
Grosse, 2008
Steingard, 2007

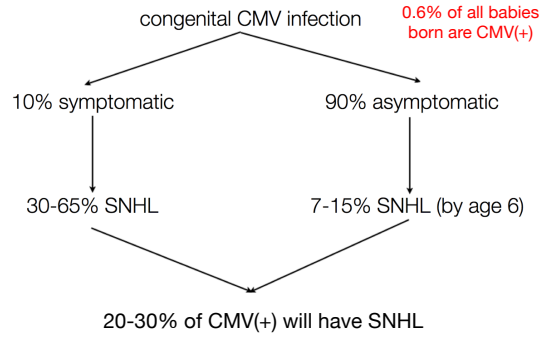
CMV hearing loss



CMV-associated hearing loss can have any pattern

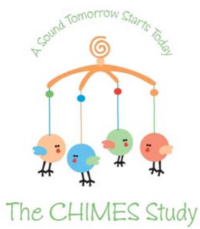
Williamson, 1992
Rosenthal, 2009
Peters, 2002
Gross, 2008
Steingard, 2007

CMV hearing loss epidemiology



0.2-0.6/1000 live births = 1000 new cases/year in the US
May be vastly underestimated

CMV prevalence CHIMES Study



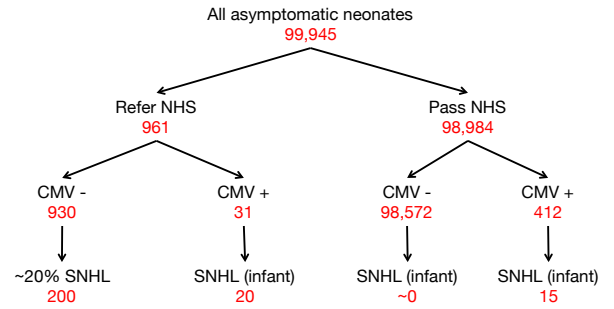
Where: University of Alabama, Mississippi, Cincinnati, New Jersey, Charlotte, Pittsburgh, UT Southwestern

Who: 100,000 newborns

What: Universal CMV screening

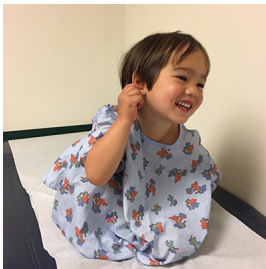
Outcomes: Congenital CMV infection and hearing loss

CMV screening CHIMES



Fowler, 2017

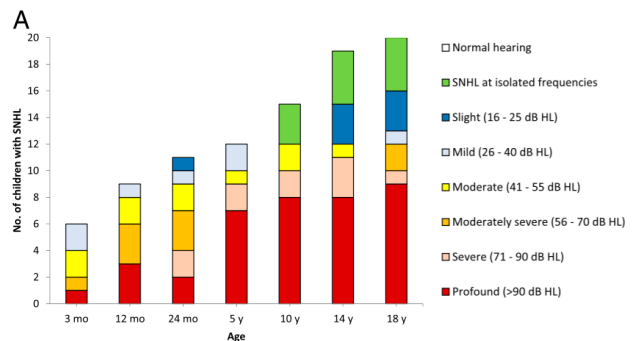
CMV Hearing loss Long-term Outcomes



18-year follow up of asymptomatic congenital CMV cohort identified by universal CMV screening

Lanzieri, 2017

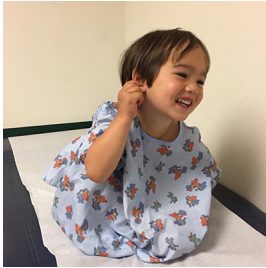
CMV Hearing loss Long-term Outcomes



Lanzieri, 2017

CMV Hearing loss Long-term Outcomes

CMV characteristics Summary



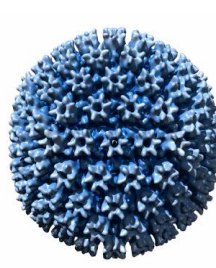
18-year follow up of asymptomatic congenital CMV cohort identified by universal CMV screening

10% with SNHL at birth
25% with SNHL by age 18

65% with progressive SNHL, with new-onset and progressive SNHL documented up to 18 years of age

89% of children with unilateral hearing loss progress to profound in that ear

75% of children with unilateral hearing loss developed hearing loss in the contralateral ear



- Highly variable
- Frequently progressive
- Onset/progression throughout childhood
- Occurs with or without other symptoms
- ONLY occurs with prenatal transmission

Lanzieri, 2017

CMV Hearing Loss

CMV Testing

Congenital CMV-associated hearing loss

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Prevalence
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Dried-blood-spot testing

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Universal newborn CMV screening
Hearing-targeted CMV screening

CMV management

Education, hygiene, and public health
Antiviral treatment
Current clinical trials



Prenatal screening healthy pregnant women
- requires multiple serologic tests
- not routinely performed

Neonatal (up to 2-3 weeks) culture or PCR from urine, saliva or blood
- gold standard

Newborn screening saliva PCR assays
- not routinely done

Postnatal PCR assay from dried newborn blood spots
- 99% specificity
- 30% sensitivity

CMV Neonatal Testing

CMV Postnatal Acquisition



Culture or PCR from urine or saliva
Gold standard test
Only reliable for congenital CMV detection up to 2-3 weeks of age

Table 1 Acquisition of cytomegalovirus infection

	Age at screening			
	6 Weeks	3 Months	8 Months	1 Year
No screened	253	249	247	234
No (%) excreting CMV	9 (3.6)	30 (12.0)	37 (15.0)	46 (19.7)

Peckham, 1987

CMV DBS testing



- Dried Blood Spot
- Guthrie Cards
- Newborn Screening
- Storage in CA

CMV DBS testing

Dried Blood Spot Real-time Polymerase Chain Reaction Assays to Screen Newborns for Congenital Cytomegalovirus Infection

Suresh B. Boppana, MD
Shannon A. Ross, MD, MSPH
Zsuzsok Novak, MD
Masako Shimamura, MD
Robert W. Tolan Jr, MD
April L. Palmer, MD
Aamina Khurood, MD
Marian C. Michaels, MD
Pablo J. Sanchez, MD
David L. Bernstein, MD, MA
William J. Bort, MD
Karen R. Fowler, DpPH
for the National Institute on Deafness and Other Communication Disorders
CMV and Hearing Multicenter Screening (CHIMES) Study

Context Reliable methods to screen newborns for congenital cytomegalovirus (CMV) infection are needed for identification of infants at increased risk of hearing loss. Since dried blood spots (DBS) are routinely collected for metabolic screening from all newborns in the United States, there has been interest in using DBS polymerase chain reaction (PCR)-based methods for newborn CMV screening.

Objective To determine the diagnostic accuracy of DBS real-time PCR assays for newborn CMV screening.

Design, Setting, and Participants Between March 2007 and May 2008, infants born at 7 US medical centers had saliva specimens tested by rapid culture for early antigen fluorescence foci. Results of saliva rapid culture were compared with a single-primer (March 2007–December 2007) and a 2-primer DBS real-time PCR (January 2008–May 2008). Infants whose specimens screened positive on rapid culture or PCR had congenital infection confirmed by the reference standard method with rapid culture testing on saliva or urine.

Main Outcome Measures Sensitivity, specificity, and positive and negative likelihood ratios (LRs) of single-primer and 2-primer DBS real-time PCR assays for identifying infants with confirmed congenital CMV infection.

Results Congenital CMV infection was confirmed in 92 of 20 448 (0.45%; 95% confidence interval [CI], 0.36%–0.55%) infants. Ninety-one of 92 infants had positive results on saliva rapid culture. Of the 11 422 infants screened using the single-primer

DBS CMV PCR
(vs saliva culture)

34.4% sensitivity
99.9% specificity

Boppana et al., JAMA 2010

CMV Testing Summary

CMV testing (CMV PCR/culture)

Is sensitive AND specific before 3 weeks
Is sensitive but NOT specific after 3 weeks
Best test before 3 weeks

CMV DBS testing

Is specific but NOT sensitive
Is the only specific test after 3 weeks
Only test after 3 weeks

CMV DBS testing

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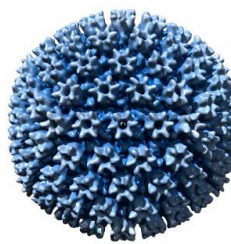
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DBS CMV PCR
(vs saliva culture)

34.4% sensitivity
99.9% specificity

Boppana et al., JAMA 2010

If positive CMV DBS – definite congenital CMV infection
If negative CMV DBS – does not exclude congenital CMV infection



CMV Hearing Loss

Congenital CMV-associated hearing loss

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Dried-blood-spot testing

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Universal newborn CMV screening
Hearing-targeted CMV screening

CMV management

Education, hygiene, and public health
Antiviral treatment
Current clinical trials

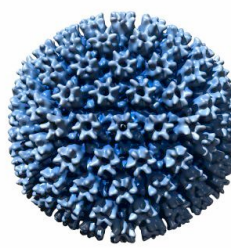


CMV Screening

Because of the drastic drop in test performance after 3 weeks, CMV-associated hearing loss is much better detected early in life

How can we identify it early?

- 1) Universal neonatal CMV screening
All babies undergo CMV testing
- 2) Hearing-targeted CMV screening
Babies who refer on newborn hearing screening all undergo CMV testing



Estimated Yield CMV screening

From an estimated 1-year cohort of babies (500,000 in California):

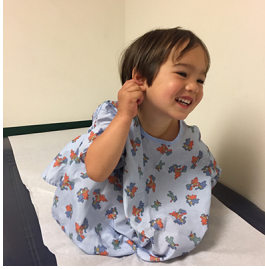
~1,000 children are born deaf/hard of hearing

Hearing-targeted CMV screening could permit definitive identification of cCMV as the cause of SNHL for 50-100 children in CA

- Surveillance
- Prognosis
- Treatment (?)

Universal CMV screening could additionally permit definition identification of cCMV and hearing loss for 100-200 children in CA

- Surveillance (JCIH guidelines)
- Prognosis
- Treatment (?)
- Earlier Identification



Hearing-targeted CMV screening

2013: Utah bill mandating CMV testing on all babies who refer on NHS



Hearing-targeted CMV screening

2013: Utah bill mandating CMV testing on all babies who refer on NHS

Outcomes From a Hearing-Targeted Cytomegalovirus Screening Program

Mariela L. Dener, PhD,* Catherine D. Zick, PhD,* Stephanie Browning-McVicar, Audi, CDCA,* Jill Bentsinger, MS, CDCASLP,* Robert H. Park, MD



Hearing-targeted CMV screening

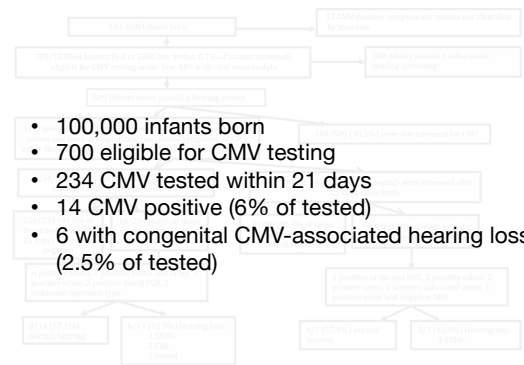
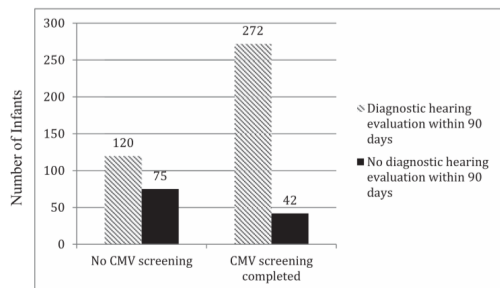


FIGURE 1
CMV testing. Results for Utah infants between July 1, 2013, and June 30, 2015. * For infants who passed NHSS had a twin who never passed a NHSS. Subsequently, both siblings were screened for CMV and found to be CMV positive. The twin with normal hearing who passed the hearing screening was not included in the analysis. SNHL, conductive hearing loss; PHL, polymorphic chain reaction.

Hearing-targeted CMV screening



Infants who underwent CMV screening were more likely to have undergone diagnostic testing within 3 months

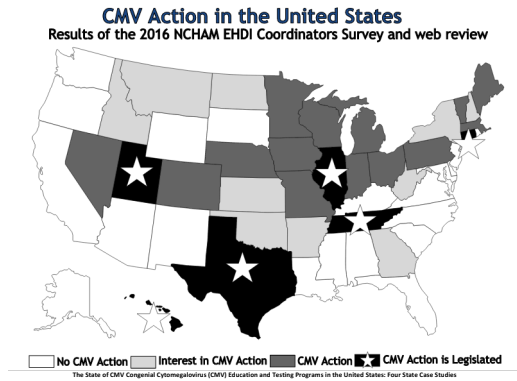
Hearing-targeted CMV screening

TABLE 3 Associations of Maternal and Infant Factors With Follow-up Diagnostic Hearing Evaluations, July 2011–June 2015 (N = 1078)

Variables	Diagnostic Hearing Evaluation by 3 Months	%
CMV testing		
Born before CMV testing mandate enacted: no CMV test	520	56.24
Born after the CMV testing mandate enacted: CMV test after 21 d	120	61.54
Born after the CMV testing mandate enacted: CMV test within 21 d	66	82.50
Born after the CMV testing mandate enacted: CMV test after 21 d	206	88.03
Born after CMV testing mandate enacted	392	77.01

Implementation of hearing-targeted CMV screening significantly improved rate of diagnostic testing completed within 90 days (56% to 77%)

HT-CMV Screening Legislation



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CMV Prevention



Most common route of transmission -> contact with saliva and urine of infected infants/toddler

- Daycare workers
- Caregivers of infants and toddlers

Risky behaviors:

- Changing diapers
- Sharing food with infant/toddler
- Poor handwashing

CMV Prevention

Education

1) Adler et al (2004)
166 seronegative (high-risk) mothers randomized to no education or hygiene and CMV education:

Reduction in maternal CMV infection rate from 42% to 6%

2) Revello et al (2015)
331 seronegative mothers received education on CMV and hygiene best practices, compared to control group

Reduction in neonatal CMV infection rate from 7.6% to 1.2%



CMV Prevention

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Reduction in neonatal CMV infection rate from 7.6% to 1.2%

Education of pregnant women is highly effective in preventing congenital CMV infection



Treatment Valganciclovir for CMV hearing loss

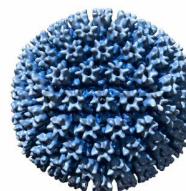
NIAID Collaborative Antiviral Study Group
Kimberlin *et al.*, *NEJM* 372(10):933-43

Multinational 31-institution Phase III randomized, controlled clinical trial

109 infants < 30 days old
Symptomatic congenital CMV
43% with baseline hearing loss

6 wks vs. 6 mos PO valganciclovir
24-month follow up

Significantly increased odds of hearing improvement or stabilization of normal hearing with 6-month course (OR (1.02-6.91) at 24 months)



THE NEW ENGLAND JOURNAL OF MEDICINE

CMV-associated SNHL [Valganciclovir trial](#)

[NCT03301415](#)

Multi-institution Phase II open-label trial

48,000 asymptomatic newborns to be screened
241 expected cCMV infants
229 expected to have normal hearing
All receive 4 mo valganciclovir

Primary Endpoint: hearing level at 6 months
Secondary Endpoint hearing level at 18 months; safety

CMV-associated SNHL [Valgan Toddler Study](#)

[NCT01649869](#)

Multi-institution Phase II randomized, controlled clinical trial

6 wks PO valganciclovir vs. placebo
Age 1 month – 4 years with sensorineural hearing loss

Congenital CMV by neonatal urine CMV or dried blood spot
CMV

CMV-associated SNHL [ValEar Trial](#)

[NCT03107871 \(ValEar Trial\)](#)

Multi-institution Phase II randomized, controlled clinical trial

Age 1 month – 6 months with congenital CMV-associated
isolated SNHL

6 mos PO valganciclovir vs. placebo

Auditory, speech, language, developmental outcomes

[Currently enrolling!](#)

CMV-associated SNHL [ValEar Trial](#)

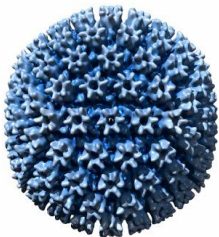
[NCT03107871 \(ValEar Trial\)](#)

- 1) Age 1-6 months
- 2) > 37 weeks gestational age at birth
- 3) Positive congenital CMV by urine culture or PCR by 21 days' age, OR Positive congenital CMV by urine culture/PCR AND positive newborn dried blood spot PCR
- 4) Confirmed SNHL by auditory brainstem response (ABR)

Exclusion criteria:

- 1) Symptomatic CMV
- 2) Parent/guardian does not speak English or Spanish

CMV Treatment [Summary](#)



CMV treatment (6 months valganciclovir):

- Can prevent progression of hearing loss
- Is of unknown efficacy in kids with isolated CMV-associated hearing loss AND in older kids
- Not currently officially recommended by AAP Red Book
- Is being discussed with parents in collaboration with ID/OHNS

CMV-associated SNHL [Current Practice - UCSF](#)

Babies under 3 weeks of age with referred NHS

- CMV testing (urine/saliva PCR or culture)
- Diagnostic audiologic testing

Babies over 3 weeks of age with referred NHS

- Diagnostic audiologic testing

Babies and children 3 weeks - 6 months of age with confirmed SNHL

- CMV urine culture/PCR
- If positive, CMV DBS testing
- If confirmed congenital CMV and SNHL, consider ValEAR trial

Children over 6 months of age with confirmed SNHL

- Consider CMV DBS testing (for etiologic workup for SNHL)
- If positive, consider prognosis in management decision-making

cCMV and SNHL UCSF Experience

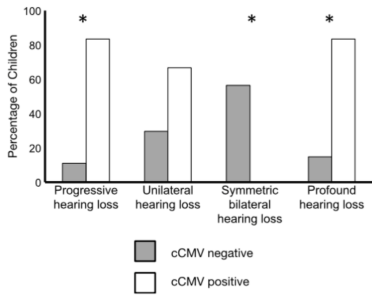
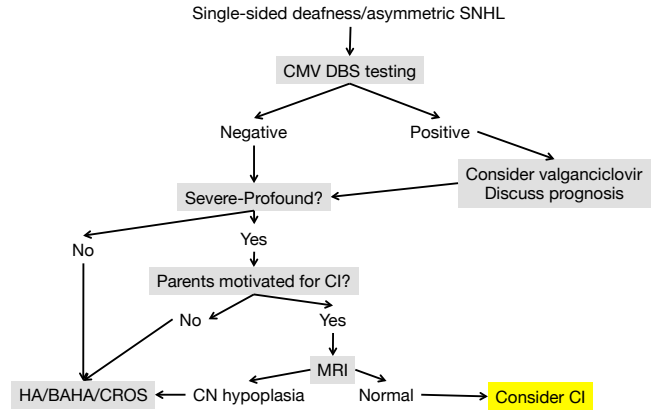


Fig. 1. Percentage of children with progressive, unilateral, symmetric bilateral, and profound (in the worse-hearing ear) hearing loss in the CMV negative versus CMV positive children (*p < 0.01).

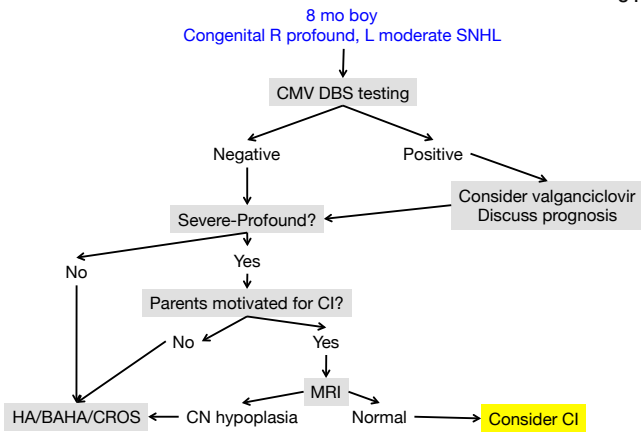
- 2 years consistent testing:
- Hearing-targeted CMV screening (~30/year)
- CMV dried-blood-spot testing (~100/year)
- 10 cases of congenital CMV-associated SNHL identified in 2 years

Lee, 2019

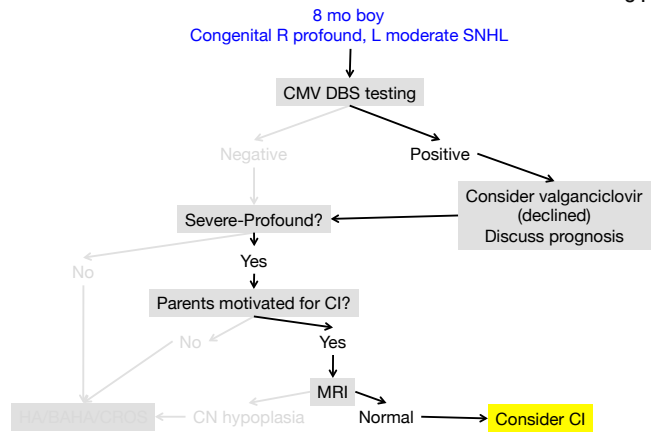
Asymmetric SNHL Testing algorithm



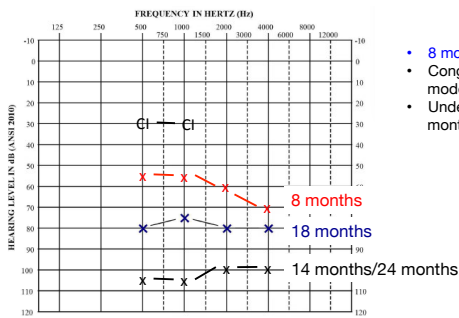
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JT

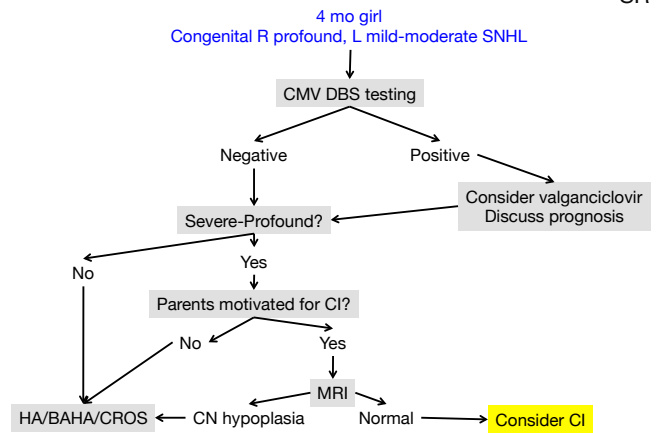


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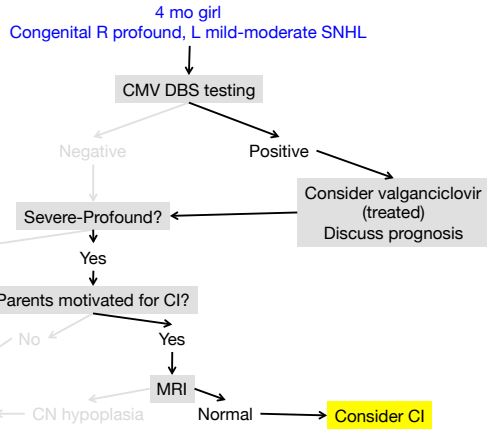


- 8 mo boy
- Congenital R profound, L moderate SNHL
- Underwent R CI at 12 months

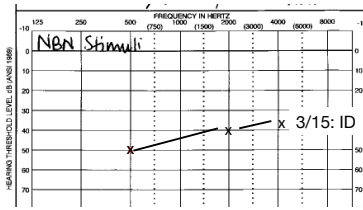
SR



SR

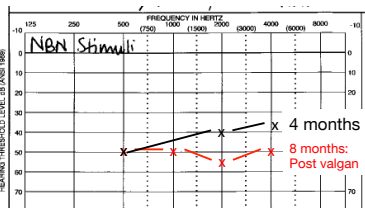


SR



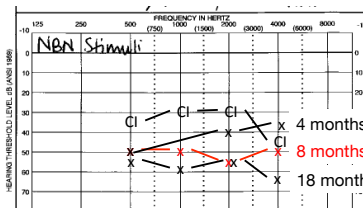
- 4 mo girl
- Congenital R profound, L mild-moderate SNHL

SR



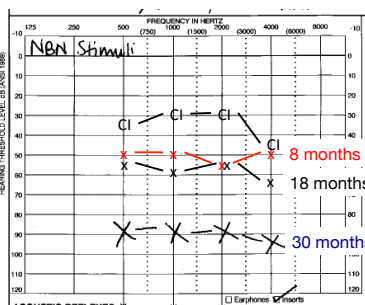
- 4 mo girl
- Congenital R profound, L mild-moderate SNHL
- 6 mo valganciclovir treatment (completed 1/16)
- Underwent R Med-EI Flex 28

SR



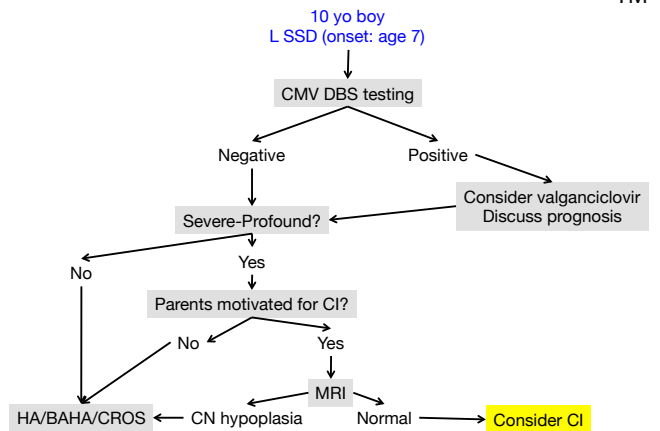
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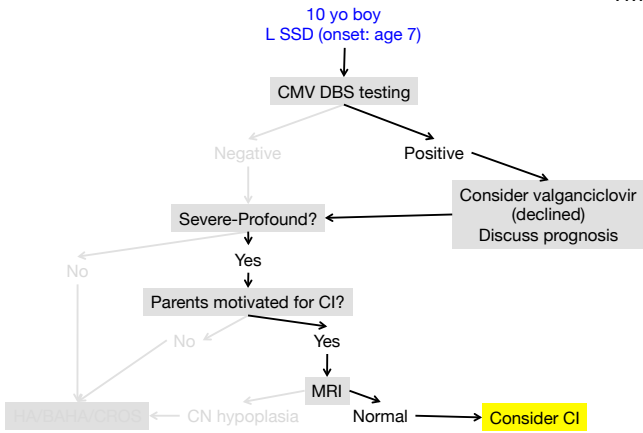


- 4 mo girl
- Congenital R profound, L mild-moderate SNHL
- 6 mo valganciclovir treatment (completed 1/16)
- 16 mo: R Med-EI Flex 28
- 2.5 yrs – drop in L hearing
- Age-appropriate speech, language, auditory skills (PLS, GFTA, LittEars)
- Underwent contralateral CI
- Impact of valganciclovir treatment?

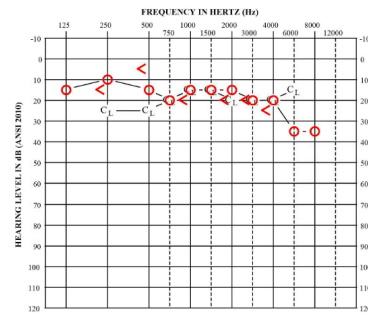
TM



TM



TM



10 yo boy
Congenital CMV

Underwent L CI
(Cochlear 532)

R slight-mild SNHL

6-month follow-up
Consistent user

AZBio 79%
CNC word 58%

Questions?

