Incorporating CMV Testing and Treatment for the Hearing Impaired Child

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Nondisclosure:

• NIDCD R01 co-I Cochlear Implantation
• NIH R01 PI CMV multi-institutional study-pending
• Valganciclovir – not FDA approved for congenital CMV
Objectives:

• Learning Objective 1: Identify the advantages and disadvantages of saliva, dry blood spot and urine CMV PCR testing in clinical practice.

• Learning Objective 2: Describe role of central nervous system imaging in infants with SNHL identified by hearing and CMV screening.

• Learning Objective 3: Assess the outcomes from antiviral therapy for CMV infected hearing impaired only infants.
Join Kahoot

• Enter “Kahoot”
• Enter the Game Pin number indicated
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Case History:

6 mo old child presents with unilateral profound SNHL? Failed right ear –NBHS
2 subsequent ABRs confirm the unilateral profound loss

What is the next step?

a. Connexin 26
b. Genetics evaluation
c. MRI temporal bone
d. CMV testing
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The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss – Utah Experience

• What happens if you look for CMV?
• May 2008 started to incorporate CMV testing
• Sequential diagnostic paradigm

“New Current” Approach to Pediatric SNHL

History, physical examination, complete audiologic work-up

- Diagnosis apparent (syndrome, AD, trauma, meningitis)
  - Appropriate treatment
  - GJB2 screen
    - Positive
      - Genetic counseling
    - Negative
      - Imaging
        - Lab tests as indicated
        - ECG (if severe to profound SNHL)
    - Imaging
      - Preferential seating
      - Serial audiograms

- Diagnosis uncertain (idiopathic)
  - Unilateral
    - CMV testing
    - Imaging
     - Preferential seating
     - Serial audiograms

- Bilateral
  - FM, HA and/or CI
  - Preferential seating
  - Ophthalmology evaluation
  - Speech therapy
  - Audiology rehabilitation
The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

• Chart and database review
• Children 3 yrs or younger
• May 2008-September 2013
• Sequential diagnostic paradigm
The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

- **Confirmed Diagnosis**: positive urine or saliva CMV PCR infant < 3 weeks OR positive result infant > 3 weeks AND positive DBS

- **Probable Diagnosis**: positive urine or saliva > 3 weeks of age AND CNS findings or progressive SNHL
The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

• Those with negative CMV testing underwent imaging, genetics evaluation +/- EKG
• Cost analysis of the diagnostic testing (Multihospital Standardized Cost Accounting System):
  MRI t-bone $1591
  GJB2 testing $611
  CMV PCR saliva or urine $66
The Role of Cytomegalovirus Evaluation in Pediatric Hearing Loss

SNHL Etiology Based on CMV, Imaging and Genetic Evaluation

Largest group with a known etiology 30%

N=83
Cost Estimates Using Different Approaches for SNHL Evaluation:

- **Mild**
- **Mod-Sev**
- **Sev-Prof**
- **Uni**
- **ANSD**
- **Overall**

Cost $/100 patients

- CMV
- Imaging
- Genetic
- Simultaneous

Type of Hearing Loss

- Mild
- Mod-Sev
- Sev-Prof
- Uni
- ANSD
- Overall
Utah Legislative Efforts:
House Bill 81 (July 2013):

- DOH public education program to inform caregivers about CMV
- DOH education for providers and other organizations offering children’s programs
- Medical practitioners to test infants < 3 wks of age who fail two newborn screening tests for CMV and inform the parents cx and rx
National Map for Hearing Targeted Early CMV Screening 2013:
National Map for Hearing Targeted Early CMV Screening 2016:

From National CMV Foundation Website March 2016
Case History:

6 mo old child presents with unilateral profound SNHL? What CMV test would you order?

a. Saliva CMV PCR
b. Blood IgM serology
c. Urine CMV PCR
d. DBS CMV PCR
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Saliva CMV testing:

• Tests the highly conserved IE 19 gene of CMV
• Testing performed at ARUP/IHC/ Mark Schleiss UM
• Validated under the WHO guidelines for clinical laboratory testing.
• Sensitivity 100%
• Specificity 99.9% ?
• Cases of false positive results! (breast milk contamination)
Urine CMV testing:

• Tests the highly conserved IE 19 or gB gene of CMV
• More difficult to obtain specimen
• Testing performed multiple laboratories: ARUP, LabCorp, Quest, PAML, IHC, Viracor-IBT Laboratories (quantitative only)
• Comparable sensitivity and specificity to saliva
Why Urine vs Saliva?

What about the cost?

- ICD-9 code: 389.8 (neonatal hearing loss)
- CPT code: 87496 (CMV detection by PCR – qualitative)
- **Saliva**: $270
- **Urine**: $100
- Typically covered by insurance carriers in US
Case History:

• 6 mo old child with unilateral profound SNHL ...Urine CMV is positive. What next?

a. Counsel the family that their child has congenital CMV
b. Counsel the family that their child has postnatal CMV
c. Recommend DBS CMV PCR
d. Recommend Valganciclovir therapy
Case History:

• 6 mo old child with unilateral profound SNHL ...Urine CMV is positive. What next?

a. Counsel the family that their child has congenital CMV
b. Counsel the family that their child has postnatal CMV
c. **Recommend DBS CMV PCR**
d. Recommend Valganciclovir therapy
How To Diagnosis CMV?

• CMV diagnosis requires lab testing within first 2-3 weeks of life!
• Reynolds et al NEJM 1973- 12/13 postnatal infection 4 weeks after birth; 1/13 postnatal infection 2-3 weeks after birth
• Needs to be confirmed?
Dry Blood Spot Testing (DBS):

- March 2007-May 2008, 20,448 infants at 7 US medical centers underwent saliva rapid culture and DBS CMV PCR testing
- 2 primer DBS PCR assay 34.4%
- sensitivity and 99.9% specificity
- DBS PCR CMV testing has low sensitivity
- May be the only way to diagnose CMV in older child!

Dry Blood Spot Testing (DBS):

- Each state keeps their DBS for different duration
- Talk to EDHI rep
- ARUP/Mark Schleiss lab has commercially available CMV PCR assay for DBS
Case History:

- 6 mo old child presents with unilateral profound SNHL? If DBS CMV PCR negative. What next?
  a. Temporal bone CT scan
  b. MRI scan
  c. Genetics evaluation
  d. Connexin testing
Case History:

• 6 mo old child presents with unilateral profound SNHL? If DBS CMV PCR negative..
  What next?
  a. Temporal bone CT scan
  b. MRI scan
  c. Genetics evaluation
  d. Connexin testing
Neurodiagnostic Evaluation

Patchy white matter lesions

Polymicrogyria
CNS Characteristics of CMV hearing impaired children:

- Thirty-three cCMV children (94%) underwent MRI or CT scan imaging of the brain.
- Twelve children (36% tested) demonstrated brain abnormalities consistent with intracranial CMV infection.
- Four children underwent both MRI and CT brain imaging. Abnormalities were detected for both modalities in three children.

Utah CMV cohort. Unpublished results
Rationale for Antiviral Therapy?

• 26 day old infant presented with CMV induced SNHL
• Failed NBHS
• Saliva CMV PCR @ 3 wks age- positive
• ABR- normal right and left profound SNHL
• MRI: bilateral perisylvian cortical dysplasia
• Ophthalmology exam- normal
Rationale for Antiviral Therapy?

- VGC x 6 weeks
- FU audio 18 mo after rx-stable hearing
- Speech progressing normally
Antiviral (VGC) treatment Hearing Impaired CMV Infected:

• 8 asymptomatic CMV patients underwent VGC + 3 axx treated before Utah law (n=11)
• Ave. age initial treatment 45± 22 days (28-101 days)
• Duration ave. 108±56 days (45-182 days)
• 3 (30%) neutropenia- 2 required reduction dose, 1 earlier cessation at 3 mo vs planned 6 mo (infected dacrocystocele).
• 4 elevation transaminase- 1 dose adjustment required
• Average follow-up period: 1.8 years (0.3-2.8)
Preliminary Outcomes from Antiviral Therapy:

- Total ears, Worse versus same, or improvement (NEJM 2015)
Need for Evidence Based Data on VGC for Asymptomatic CMV infected and hearing impaired Children:

• Compare hearing and language outcomes of CMV infected hearing impaired only infants
• Placebo versus Valganciclovir x 6 mo
• NIH application- probably funded 😊
• 21 multi-institutional study
Conclusion:

• Rapidly evolving field
• CMV testing can be incorporated into a clinician’s practice
• Diagnosis not difficult
• May be more cost effective as first test
• May identify CNS abnormalities
• Antiviral therapy may be an option