Congenital Cytomegalovirus: A Pilot Study

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Objectives

1) Congenital cytomegalovirus (cCMV) basics
2) Minnesota CMV pilot study
3) CMV and newborn screening – the case for CMV
4) Questions
Cytomegalovirus (CMV) Basics

• It is the MOST common congenital viral infection in the USA
• Common cause of disability
• Infection rate is 0.6-0.7% of live births worldwide
• 15-20% of infected infants have permanent disability
• 6,000 children in the U.S. annually
• Low awareness – clinical impact mostly discussed with organ transplant recipients or HIV-infected individuals
Congenital Cytomegalovirus (cCMV) Infections

• Most common cause of non-hereditary sensorineural hearing loss in children

• Three possible classifications for cCMV
  • Symptomatic – 10-15%
  • Asymptomatic with hearing loss (may or may not be present at birth) – 7-15%
  • Asymptomatic with no clinical concerns – 80%

• Can be treated with antiviral medication if identified early (ganciclovir and/or valganciclovir)

• Congenital vs acquired – distinguishable only within first 21 days of life
Impact of cCMV

- Prenatal findings can include: echogenic bowel, IUGR, ventriculomegaly, thick placenta
- Newborns can show: prematurity, liver disease, petechiae, thrombocytopenia
- Symptomatic children can present with:
  - Criteria – 2 or more features with CNS involvement
    - Cognitive impairment/mental disability – 55-66%
    - Vision loss – 22-58%
    - Hearing loss – 30-50%
    - Microcephaly
    - Cerebral palsy
    - Seizures
    - Death

* Advocates have dubbed CMV the “birth defects virus”
Burden of CMV

Cannon et al., 2004

Annual Number of U.S. Children with Long-Term Sequelae

- Congenital CMV disease
- Fetal alcohol syndrome
- Down syndrome
- Spina bifida/anencephaly
- Pediatric HIV/AIDS
- Invasive Hib
- Congenital rubella syndrome
By the Numbers

Minnesota – birth rate of ~70,000 per year

*assume an infection rate of 1/200

~350 newborns each year are born infected

Symptomatic:
- 35 infants

Asymptomatic with hearing loss:
- 35 infants

Asymptomatic:
- 280 infants
Minnesota Study

• Funded through CDC’s Emerging Infection Program (EIP) Cooperative Agreement

• Partnerships with:
  • CDC – Sheila Dollard, PhD,
  • UMN – Mark R. Schleiss, MD
  • Hospitals: Fairview Health (UMMC, Ridges, Southdale) & Allina Health (Abbott Northwestern & United)
Study Aims

• Clinical sensitivity:
  • Compare two DBS PCR assays performed in independent laboratories (CDC/Dollard and UMN/Schleiss laboratory), using the newborn DBS as a source of CMV DNA
  • Compare DBS PCR results to PCR performed on saliva specimens obtained in the newborn nursery
    • Viral load is known to be higher in urine and saliva
  • These results will help clarify which assay is more useful for universal newborn CMV screening
• Target enrollment: 30,000 infants
Study Design

Demographics collected:
- GA at delivery
- Living children (TPAL)
- Birth weight
- Head circumference
- Race
- Ethnicity

Consents sent to MDH for processing

Saliva swab to UMN/Schleiss lab (weekly)

Obtain parental consent and saliva sample in nursery

3 DBS punches to CDC (weekly)

3 DBS punches to UMN (weekly)

Results into Database

Positive Results?

MDH GC contacts PCP and f/u initiated

Clinical Evaluation by Dr. Schleiss

4 years of medical record review for CMV features

No action needed
Clinical Evaluation

• Infant is evaluated by pediatric infectious disease provider familiar with CMV (to date all infants have seen Dr. Schleiss)
  • Hearing evaluation
  • History and physical exam
  • CNS imaging (selected)

• Positive infants upon clinical evaluation
  • Additional labs obtained for confirmation (Urine)
  • Parents are engaged in a discussion regarding treatment options
  • Hearing assessments at increased frequency – every 3 mo for first 3 years, and every 6 mo until age 4
  • Medical record review annually until age 4
First site began enrolling mid-February 2016

5 sites active with enrollment

Total of **3,395** infants enrolled

Enrollment rate: 55% overall, 72% when discussed

Number of positive infants: 10

Initial clinical evaluation of positive infants:

- 4 infants – symptomatic with hearing loss
- 6 infants – asymptomatic without hearing loss (at initial evaluation)

Delayed hearing loss:

- 1 ‘asymptomatic’ infant developed hearing loss (mild to moderate unilateral) identified on 6 month hearing assessment
The Case Against Universal Screening

• Lack of awareness of CMV

• So. Many. Babies.
  • This is a HUGE increase in follow-up burden (min. 350 infants per year)

• Asymptomatic infants/children – 80% of those identified
  • Persistent parental anxiety (fragile child syndrome)
  • Unnecessary medical attention
• Treatment options
  • Ganciclovir and Valganciclovir are off-label for cCMV
  • Only treat some of the features – moderately favorable effect on long-term audiologic and neurodevelopmental outcomes in symptomatic children
  • Consensus papers recommend treating symptomatic children – not currently the recommendation for “asymptomatic with hearing loss” children but is occurring clinically

• A vaccine is a better option...

• Lack of validated laboratory method for dried blood spots (DBS)
  • CHIMES study found DBS detection of CMV was low (~ 30% sensitivity) however, their DBS method was proven to be low yield and out-of-date
The Case For Universal Screening

- Most CMV-associated disability not evident at birth and therefore not detected
  - Symptomatic infants missed
- Early intervention improves outcomes for these infants
  - Increased monitoring
  - Non-pharmaceutical therapies become an option
- Good evidence for benefit with antiviral tx for symptomatic infants
- CMV screening would avoid diagnostic odyssey for newborns with symptoms
• Targeted approaches fall short
  • Utah example: Misses delayed onset hearing loss therefore misses opportunity for treatment

• EHDI programs are unequipped to deal with a laboratory testing platform

• 10 years since CHIMES
  • Technology has changed and improved

• Advocates are organized
  • Universal saliva collection would be EXPENSIVE
  • DBS may be ‘good enough’
Does it Meet Criteria?

• Medically serious condition with well described case definition
  • Yes
  • However, with 80% unaffected cCMV is unlike any other disorder on the NBS panel

• Accurate, high throughput diagnostic test available
  • No, not currently – working on it

• Effective treatment available
  • Yes - early intervention and promising antiviral treatments for symptomatic newborns
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“If you don’t pass, Screen”

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