Screening for Congenital Cytomegalovirus (CMV) Infection and Hearing Loss as an Adjunct to EHDI Programs

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CMV and EHDI

- Early Hearing Detection and Intervention (EHDI) is more than just newborn hearing screening
- Many children with late-onset or progressive hearing losses are not detected by newborn hearing screening
- Congenital CMV is leading cause of late-onset hearing loss
- Screening for congenital CMV could lead to earlier detection of late-onset hearing losses
Overview

- Background on congenital CMV
- CMV and hearing loss
  - Prevalence of hearing loss
  - Attributable fraction of hearing loss
- Methods to screen for congenital CMV
Cytomegalovirus (CMV) infection

- CMV is spread through bodily fluids, e.g. saliva
  - Main exposure is young children
- Majority seropositive for CMV
  - NHANES III data (Staras, 1996)
  - Seropositivity 36% at 6-11 years, 91% at 80+ years
  - Overall seropositivity ages 6+ is 59%
    - Non-Hispanic white 51%
    - Non-Hispanic black 76%
    - Mexican-American 82%
Congenital CMV

- Overall prevalence of congenital CMV 0.4% to 1.2% of newborn infants
  - Most common perinatal infectious disease
  - Varies by SES and ethnicity

- Transmission depends on CMV status of mother
  - Primary infection in seronegative women
    - High risk of transmission
  - Recurrent infection in seropositive women
    - Lower risk of transmission
About 10-15% have symptoms at birth, although often not detected
- Perhaps 50% develop sequelae
  - Mental retardation, hearing loss, visual impairment, etc.
  - Multiple impairments common

Asymptomatic infants also at risk
- About 10-15% develop sequelae, mostly hearing loss (Dollard, 2007)
CMV and Hearing Loss

- Sensorineural hearing loss (SNHL) occurs in 10-15% of children overall according to systematic review (Dollard et al., 2007)
  - 11% of children without symptoms at birth
  - 35% of children with symptoms at birth
- Many losses are progressive or late-onset
Laterality and Level of Hearing Loss in Congenital CMV

• How many children have bilateral SNHL?
  – 9.3%, or 60% of those with CMV (Dahle, 2000)
  – 3.5%, or 34% of those with CMV (Ross, 2006)
  – 94% of those with CMV (Ogawa, 2007)

• Moderate to profound bilateral SNHL
  – 5% with bilateral SNHL at 50 dB (Hicks, 1993)
Late-Onset HL in Congenital CMV

- Fraction of SNHL detectable at birth
  - 1/3 in UAB study at 20 dB threshold (Fowler, 1999)
    - 5.2% SNHL detected at birth
    - 15.4% SNHL at age 6 years
  - 1/2 in UAB study at 30 dB threshold (Fowler, 1999)
    - 3.9% SNHL detected at birth
    - 8.3% SNHL detected at 6 years
Moderate-Profound Bilateral SNHL and CMV

- At least 30,000 infants born with congenital CMV in US (0.7% of 4.1 million)
- 3,000 to 5,000 have SNHL (10-15%)
- 1,000 to 3,000 have bilateral SNHL $\geq$ 20 dB (34-60%)
- 500 to 2,700 have bilateral SNHL $\geq$ 40 dB (50-90% of those with bilateral HL)
CMV-Attributable Fraction of SNHL

• What fraction of permanent hearing loss in children is due to congenital CMV?
  – Most studies report <4%, based on symptomatic cases and HL detectable at birth (Morzaria, 2004; Dent, 2004)
  – Some attribute 30% of SNHL to congenital CMV (Fowler, 1995; Barbi, 2003; 2006; Fowler, 2006)
  – Best estimate is 15-20% (see next slides)
CMV-Attributable Fraction of SNHL: Empirical Evidence (1)

- **Sweden study (Harris, 1984; Ahlfors, 1999)**
  - According to Harris (1984) 4 of 10 (40%) children with profound bilateral HL had congenital CMV.
  - Ahlfors (1999) reported rate of profound bilateral hearing loss 57% as high in complete cohort, implying attributable fraction of 23%.

- **Texas study (Ohlms, 1998)**
  - 21 of 118 (18%) children with HL had CMV, apparently based on assay of samples taken after birth but no details provided.
CMV-Attributable Fraction of SNHL: Empirical Evidence (2)

- Italy study (Barbi, 2003)
  - 22 of 130 (17%) children with bilateral HL > 40 dB
    - 9 of 87 (10%) with HL detected soon after birth
    - 13 of 43 (30%) with HL of unknown causes detected >3 months after birth
CMV-Attributable Fraction of SNHL: Empirical Evidence (3)

- Japan study (Ogawa, 2007)
  - Families of children with SNHL diagnosed as university clinic asked to bring in dried umbilical cord specimens stored as Japanese custom
  - 10 of 67 (15%) with any SNHL
    - 9 of 55 (16%) with bilateral SNHL at 55 dB threshold
    - 8 of 36 (22%) with profound SNHL (>90 dB)
  - 21 of 67 (31%) with a known genetic risk
    - 9 of 67 (24%) with GJB2 mutation
Implications for EHDI Programs

- Congenital CMV is a leading cause of hearing loss
  - Second to GJB2 (Connexin 26) mutations
  - About 15-20% of all childhood SNHL

- About half of all HL due to CMV is not detectable by UNHS

- Screening for CMV could result in the detection of HLs missed by UNHS
  - How feasible is detection?
Potential Methods for Congenital CMV Screening

- Urine or saliva specimens
  - Gold standard for detection
  - Requires hospital laboratory to perform assay
  - No public health infrastructure

- Dried blood spot (DBS) specimens
  - Public health NBS system
  - No specimen collection cost
  - High-throughput laboratories can lower cost
  - Uncertain sensitivity
Two Methods to Detect CMV in DBS Specimens

- **IgM assay**
  - Presence of CMV-specific IgM antibodies indicates infection with CMV in utero

- **PCR assay**
  - Used to detect viral DNA
  - Genome copy number indicates viral load
CMV Viral Load Associated with Hearing Loss
(Boppana, 2005)

% with Hearing Loss

CMV / ml WB

Copies CMV / 3 mm punch
<10 10-80 >80

Copies CMV / PCR reaction
<2 2 – 16 >16

P < 0.001

10 / 25
2 / 25
0 / 25

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Validation of PCR Assay for CMV Viral Load: California-CDC Study

- 5000 Newborn DBS (50% Latino)
- 1.2 cm DBS received per newborn
- 6 mm punch for CMV IgG and limited IgM testing
- 6 mm punch for nucleic acid extraction CMV and PCR
- Partial results indicate high sensitivity of PCR assay, about 1% prevalence
Evaluation of CMV Screening Options

• Trade off between sensitivity and cost
  – IgM assay
    • Less sensitive, perhaps 70-80%
    • Less costly, <$5 per specimen
  – PCR assay
    • Appears highly sensitive
    • Relatively costly, >$10 per specimen

• More work needed to assess analytical validity
Utility of CMV Screening

• EHDI goals
  – Prompt identification of hearing loss in young children
  – Prompt referral for intervention
    • Early intervention services
    • Amplification or other option

• Expected benefit of CMV screening
  – Early identification of children with late-onset or progressive hearing loss
  – Improved language development and school outcomes


References (2)


