Highlights from the 2008 Congenital CMV Conference

Scott D. Grosse, Danielle S. Ross, Sheila Dollard, Michael J. Cannon

Centers for Disease Control and Prevention

National Center on Birth Defects and Developmental Disabilities

Background

- Congenital CMV is the leading non-genetic cause of childhood hearing loss in the US
- Approximately 15-20% of cases of permanent bilateral moderate hearing loss in children are due to congenital CMV (Grosse, Dollard, Ross, JCV 2008)
  - Perhaps 25% of bilateral profound hearing loss among children is attributable to congenital CMV

Overview

- Second international congenital CMV conference held in Atlanta, November 7-8, 2008
  - Michael Cannon and Lenore Pereira co-chairs
  - Co-sponsored by CDC and the Congenital CMV Foundation
- Distinctive emphasis: public health
  - Epidemiology
  - Prevention
  - Newborn screening
- Two conference tracks
  - Scientific
  - Family

Opening Plenary Session: Challenges and Solutions

- **Michael Cannon**, CDC
  - Summary of epidemiology of congenital CMV
- **Gail Demmler-Harrison**, Baylor College of Medicine
  - public health action and need for awareness, prevention, and treatment
- Three parent advocates
  - **Tracy McGinnis**
    - Founder Brendan B. McGinnis Congenital CMV Foundation
  - **Jenny Bailey and Caroline Bailey**
    - Caroline has been deaf since birth due to CCMV
  - **Lisa Saunders**
    - Daughter Elizabeth Saunders severely affected by CCMV

Family Sessions: Overview

- Geared towards needs of families who have members with congenital CMV
- Presentations by
  - Family members
  - Specialists in the fields of congenital CMV research and clinical care
  - Experts in fundraising and advocacy
- Presence of families helped raise awareness of and motivate scientists and public health personnel; also gave a boost to the burgeoning grass roots movement

Family Sessions: Parent Perspectives and Organization

- Several sessions led by family members of children affected by CMV
  - Guilt
  - Frustration at not having been told about CMV and how to reduce the risk of congenital infection
  - Lack of awareness
  - Lack of resources available to families with child(ren) affected by CMV

Topics Covered in Presentation

- Prevalence and risk factors
- Hygiene education and pregnancy
- Prenatal testing and therapy
- Neurological and sensory sequelae
- Antiviral therapy and side effects in infants
- Vaccine development
- Newborn screening

Prevalence and Risk factors

- CDC-California study of stored blood spots (n=~4000) – Dollard and Kharrazi
  - Race/ethnicity
    - 1.0% Black
    - 0.8% Hispanic
    - 0.7% White
    - 0.6% Asian
  - Birth weight
    - 2.4% LBW
    - 0.6% ≥2500 g

Maternal Risk Factors

- Prospective French study -- Valoup-Fellous
  - Of 14 cases of congenital CMV, 13 born to mothers exposed to young children at home or at work
  - By seroprevalence in early pregnancy
    - 3 primary infections
    - 11 recurrent infections

Prevention of CMV Transmission through Good Hygiene

BOX. CDC and American College of Obstetricians (ACOG) recommendations for reducing risk for cytomegalovirus (CMV) infection

CDC recommendations for women who are pregnant or might become pregnant*

- Wash hands often with soap and water, especially after contact with saliva of or diapers from young children. Wash well for 15–20 seconds.
- Do not kiss children aged <6 years on the mouth or cheek. Instead, kiss them on the head or give them a hug.
- Do not share food, drinks, or utensils (spoons or forks) with young children.

ACOG recommendations for obstetricians and gynecologists on counseling pregnant women†

- Advise careful handling of potentially infected articles, such as diapers.
- Advise thorough handwashing when around young children or immunocompromised persons.
- Explain that careful attention to hygiene is effective in helping prevent CMV transmission.

* Available at http://www.cdc.gov/cmv.

† American College of Obstetricians and Gynecologists. Perinatal viral and parasitic infections. ACOG Practice Bulletin 20. 20th ed. Washington, DC: American College of Obstetricians and Gynecologists; 2000.

Hygiene Education and Pregnancy

- Prospective French study– C. Valoup-Fellous
  - 1,955 women seronegative at ~12 weeks of gestation received hygiene education
  - 5 women seroconverted (0.26%)
    - one-fourth as many as expected
- Prospective study in Virginia – Beth Marshall
  - 60 women with infant or toddler <2 planning another birth received hygiene education
  - 23 became pregnant, of whom 8 had toddler shedding CMV
    - 2 were already seropositive
    - 0 of other 6 seroconverted

Prenatal Screening for CMV

- Prenatal screening for CMV is not recommended in any country, but is widespread in Italy, Belgium (Brussels), and Israel
- Controversial issue – no consensus among experts at conference
- RCT data showing benefit needed

Hyperimmune Globulin (HIG) Therapy in Pregnancy

- Women who seroconvert in pregnancy at high risk (30-50%) of transmitting CMV to fetus
- Hyperimmune globulin treatment strengthens maternal immunity
  - HIG associated with 60-90% lower maternal-to-child transmission of CMV in one study (Nigro et al., 2005)
  - HIG may reduce sequelae other than hearing loss – Stuart Adler
- Randomized trial of prenatal screening and HIG therapy underway in Italy to test efficacy of HIG to prevent CCMV

Symptomatic Congenital CMV

- About 10 to 15% of children with CCMV have symptoms at birth
- Children with symptomatic infections are very likely to develop sequelae (~80%)
  - Brain damage apparent on neuroimaging studies with classical signs, e.g., intracranial calcification
  - Developmental delay and disability
  - Permanent hearing loss
- Most children with symptoms are not clinically recognized as having CCMV

CCMV and Intellectual Disability

- Japanese study of dried umbilical cords – Shin Koyano et al.
  - 20 children with IQ < 70 and no known etiology
    - ~50% of children with low IQ have no known cause
  - 5 (24%) positive for congenital CMV
    - 3 of 9 (33%) with hearing loss
    - 2 of 11 (18%) with normal hearing
    - 4 (80%) had intracranial calcification characteristic of symptomatic CCMV
    - 1 may have been asymptomatic

Asymptomatic Congenital CMV

- Two new neuroimaging studies using computed tomography (CT scans) were presented
  - 0 of 99 infants at Baylor had classical signs of CMV
  - 1 of ~80 Brazilian infants had classical signs of CMV
- Previous studies of neurodevelopment in asymptomatic CCMV
  - Developmental delay or disability
    - 0 of 35 children in Italy (Lanari et al., 2005)
    - 0 of 18 children in US (Conboy et al., 1986)
    - 4 of 49 children in China (Zhang et al., 2007)
- 5-10% of children develop permanent hearing loss

Antiviral Therapy in Infants with Symptomatic Infections

- Ganciclovir antiviral administered intravenously
  - 2003 trial of 6-week course
    - 2/3 reduction in hearing loss at 12 months
    - serious side effect of neutropenia
- Oral version (valganciclovir)
  - 2008 trial of 6-week course
    - Similar efficacy
    - Lower toxicity
  - Trial of 6-month course underway - Kimberlin
  - Observational study in Italy – Nigro
    - 6-week and 6-month oral courses effective for hearing loss
    - 6-month course more effective for developmental delay

CMV Vaccine Development

- CMV glycoprotein B (gB) vaccine – Bob Pass
  - Recently completed phase II double-blinded, placebo-controlled clinical trial
  - 441 seronegative young mothers enrolled
  - Infections assessed every 3 months
  - Findings
    - Vaccine reduces rate of infection by ~50%
    - Effective for at least 42 months
  - Results for prevention of congenital CMV not presented

Immunization and Prevention of Mother-to-Child CMV Transmission

- Two types of immunization – Ed Mocarski
  - Prophylactic – to prevent primary infection and seroconversion during pregnancy
  - Therapeutic – to boost antibody and/or T cell immunity needed to boost natural memory immune response to CMV and prevent transmission to fetus
- Reinfection during pregnancy responsible for majority of congenital CMV
  - Greater focus on CMV seropositive women required
  - Therapeutic vaccine strategies needed

Newborn Screening Overview

- Rodney Howell discussed Secretary's Advisory Committee approach to considering new disorders for core screening panel
  - Requires high throughput assay using dried blood spot (DBS) specimen
- Scott Grosse discussed alternative options for CCMV screening
  - Public health lab screening
  - Hospital-based screening
    - Urine or saliva assay
    - DBS assay

Rationale for CMV Newborn Screening

- Enable antiviral therapy
  - Not recommended for asymptomatic infants because of side effects
  - Recommended for symptomatic infants who may be missed without screening
- Identify infants requiring periodic monitoring for hearing loss
  - Early intervention when hearing loss detected

Challenges for CCMV Screening – Test Characteristics

- Requirements for acceptable CMV DNA assay using DBS specimens
  - Sensitivity ≥75%
  - No more than fraction of one DBS
  - High throughput assay for use in public health laboratory
  - Acceptable cost

Challenges for CCMV Screening – Showing Benefit

- Congenital CMV differs from other NBS disorders
  - Screening not for disease but for a risk factor
  - Only a minority of those identified likely to benefit
- Does early intervention for developmental delay improve developmental outcomes?
- Does early identification of late-onset hearing loss improve language outcomes?
- Is there an effective, safe treatment to prevent sequelae?
- What are the risks of psychosocial harm to families?

Conclusions

- Congenital CMV is a leading cause of hearing loss and developmental disability in children
- It is preventable NOW
  - Preconception and prenatal education needed
- Newborn screening should soon be feasible but research and pilot screening studies needed
- Prenatal and postnatal treatments are being tested in clinical trials
- Immunization is important future strategy