Sensorineural hearing loss in children with asymptomatic congenital CMV infection (AcCMV) up to 18 years of age.

Houston Congenital CMV Longitudinal Study

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Background

- In the United States, an estimated 25,000 – 35,000 infants are born with asymptomatic congenital cytomegalovirus (AcCMV) infection every year.

- Sensorineural hearing loss (SNHL) occurs in ~11% of children with AcCMV infection detected by newborn screening (Dollard et al. 2007).

- Long term outcomes of SNHL in AcCMV through adolescence are unknown.

Objective

- To assess hearing outcomes in children with AcCMV infection and uninfected controls followed for up to 18 years
The Houston Congenital CMV Longitudinal Study

- During 1982-1992, newborns with cCMV infection were identified through hospital-based screening
  - Culture of urine obtained within 3 days of life
  - Newborns with AcCMV infection: no CMV-related symptomatology at birth
  - CMV-negative children enrolled as controls
Method for Screening Newborns for Congenital CMV Infection

- Newborn urine samples were collected by U-bag from all newborns at TWHT, transported on ice to CMV Lab at BCM
- Urine samples were pooled 3:1
- Inoculated onto HFF tubes (2)
- Examined daily for CMV characteristic CPE
- If 3:1 pool positive, then each of the three urines were inoculated separately to determine the CMV positive urine in the 3:1 pool
- Second urine was collected from CMV positive screened newborn to confirm CMV positive culture

Newborn screening for congenital CMV infection

Evaluation in the newborn period

Enrollment in the longitudinal study

32,543 Newborns screened for congenital CMV infection during 1982-1992

135 (0.4%) CMV+ newborns

32,408 CMV- newborn controls

256 CMV- newborn controls not followed in longitudinal study

90 newborns with congenital CMV infection identified through referrals during 1982-2003

96 CMV+ newborns enrolled as cases

44 CMV- newborns enrolled as controls

7 newborns without congenital CMV infection identified through referrals during 1982-2003

186 newborns with congenital CMV infection enrolled as cases

109 AcCMV

77 ScCMV

51 newborns without congenital CMV infection enrolled as controls
<table>
<thead>
<tr>
<th>Status at birth</th>
<th>Ascertainment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>4</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>92</td>
<td>17</td>
<td>109</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>90</td>
<td>186</td>
</tr>
</tbody>
</table>
## Schedule of Follow up Evaluations, Tests and Procedures

### AGES AND GRADES

**Key Periods of Development**
- 4-6 weeks
- 4-6 months
- 9-12 months
- 18-24 months
- 2 to 5 years
- 6 years
- Grades K to First
- End First Grade
- Grades Second to Fifth
- Middle School Seventh-Eight Grade
- High school Junior/Senior
- College/Trade School Graduation
- Adult 22-29 years
- Adult 30-39 years

### EVALUATIONS AND PROCEDURES

**Age, Developmentally and Sensory Appropriate Evaluations**
- Growth measurements (weight, length, height, head circumference)
- *Hearing tests (ABR, OAE, Pure Tone Audiometry,)*
- Vision tests and Ophthalmology eye/retina exam
- Neurological and developmental exams
- Cognitive and language evaluations (Bayley, Symbolic Play, Pre-school Language Scales, Peabody Picture Vocabulary Test, WISC III, WASI, KABC, Leiter)
- Language and Academic Evaluations (Woodcock-Johnson, EOWPVT-R, PPVT-R)
- Behavioral assessments (BASC parent rating and child self report)
- Quality of Life Inventory
- Urine CMV culture
Audiologic Follow-up

- Long term follow-up included serial, age appropriate, developmentally appropriate audiological evaluations performed during infancy, childhood, and adolescence
  - Otoscopy – to evaluate for ear canal obstruction/ear wax
  - Tympanometry – evaluate for middle ear fluid/effusion
  - Otoacoustic emissions (OAE) - all subjects
  - Auditory brainstem response- infants and cognitively impaired
  - Pure tone audiometry (0.25,0.5,1,2,3,4,6,8 kHz) all frequencies
  - dB 15 to 80-90 thresholds
  - Speech testing- if age and cognition appropriate
Classification of SNHL Based on Age at Diagnosis

- **Congenital SNHL**
  - Diagnosed at the first ABR evaluation
    - **Confirmed**: when first ABR done within 3 mo. of life
    - **Presumed**: when first ABR done between 3-12 mo.

- **Delayed-onset SNHL**
  - Diagnosed during follow-up in a previously unaffected ear
  - Diagnosed after 1 year of age when that was the first evaluation
Laterality and Severity of SNHL

- **Laterality**: unilateral or bilateral
- **Degree of hearing loss** *(American Speech-Language-Hearing Society)*
  - Based on the PTA average of 0.5, 1, 2, 4 kHz:
    - Normal: -10 to 15 dB
    - Slight: 16 to 25 dB
    - Mild: 26 to 40 dB
    - Moderate: 41 to 55 dB
    - Moderately severe: 56 to 70 dB
    - Severe: 71 to 90 dB
    - Profound: 91 dB or greater
Hearing Threshold Variability Definitions

- Assessed for each ear with SNHL
- Consecutive exams, excluding those with middle ear disease
- Hearing change or fluctuations
  - Criteria adapted from ASHA 1994:
    - ≥20 dB in any frequency
    - ≥10 dB in the 4PTA, or any other 2 or 3 adjacent frequencies
    - Non-response in 3 adjacent frequencies
  - Categorized as improvement or deterioration or stable
Hearing Threshold Variability Categories

- **Progressive**
  - Overall hearing deterioration without intermittent improvement

- **Fluctuating progressive**
  - Overall deterioration with intermittent improvements

- **Fluctuating non-progressive**
  - No change between first and final exams with intermittent improvements or deteriorations

- **Stable**
  - No change and no intermittent improvement or deterioration
AcCMV – Progressive Hearing Loss - Data Collection
Data Entry
Excel Spreadsheet Screenshot
Audiology Data AcCMV Subject
Unilateral Progressive SNHL

<table>
<thead>
<tr>
<th>PID</th>
<th>Date of Birth</th>
<th>Date of evaluation</th>
<th>Gender</th>
<th>Subject Type</th>
<th>Age at Evaluation</th>
<th>RE 500 Hz Tone</th>
<th>RE 500 Hz Tone</th>
<th>LE 500 Hz Tone</th>
<th>LE 500 Hz Tone</th>
<th>LE 250 Hz Tone</th>
<th>LE 250 Hz Tone</th>
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<tbody>
<tr>
<td>81</td>
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<td>11/9/1988</td>
<td>Female</td>
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<td>0.23</td>
<td>20</td>
<td>20</td>
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<td></td>
<td></td>
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<tr>
<td>94</td>
<td>8/17/1988</td>
<td>7/1/1990</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>1.92</td>
<td>20</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>97</td>
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<td>7/8/1992</td>
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<td>Asymptomatic</td>
<td>3.99</td>
<td></td>
<td></td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>999</td>
</tr>
<tr>
<td>100</td>
<td>8/17/1988</td>
<td>5/1/1995</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>6.70</td>
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<td></td>
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<td>10</td>
<td>3</td>
<td>999</td>
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<tr>
<td>101</td>
<td>8/17/1988</td>
<td>9/12/1996</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>7.82</td>
<td></td>
<td></td>
<td>5</td>
<td>3</td>
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<td>8/5/1997</td>
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<td>Asymptomatic</td>
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<td></td>
<td></td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>999</td>
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<tr>
<td>103</td>
<td>8/17/1988</td>
<td>8/5/1998</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>9.80</td>
<td></td>
<td></td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>999</td>
</tr>
<tr>
<td>104</td>
<td>8/17/1988</td>
<td>8/8/2002</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>23.97</td>
<td></td>
<td></td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>999</td>
</tr>
<tr>
<td>105</td>
<td>8/17/1988</td>
<td>8/27/2008</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>27.88</td>
<td></td>
<td></td>
<td>15</td>
<td>10</td>
<td>3</td>
<td>999</td>
</tr>
</tbody>
</table>
Data analysis

- **Follow-up through 18 years of age**
  - Natural history description
  - Comparison of cases with controls

- **Kaplan-Meier method**
  - Probability of SNHL over time
  - Accounted for loss of follow-up
  - Group comparisons: hazard ratio (95% confidence intervals)
  - Statistical significance: log-rank test (p-value <0.05)
  - Software: SAS version 9.3 [BCM and CDC analysts]
RESULTS
Cohort of Children with AcCMV Identified through Newborn Screening and Controls

- 92 children with AcCMV
  - Median of 8 evaluations per subject, range = 1-17
  - **First evaluation** (n=92)
    - Median age = 2 mo, range = 4 days-11.5 mo
    - 6 children lost to follow-up after first evaluation
  - **Last evaluation** (n=86)
    - Median age = 17 yrs, range = 9 months-18 yrs,
- 51 control-children
  - Last evaluation at 16 years, range: 1 month-18 years
<table>
<thead>
<tr>
<th>Group</th>
<th>Age at first audiological evaluation</th>
<th>Age at last audiological evaluation</th>
<th>Number of evaluations per subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children with AcCMV (n=92)</td>
<td>2 mo. (4 days-11.5 mo.)</td>
<td>17 yrs. (23 days-18 yrs.)</td>
<td>8 (1-17)</td>
</tr>
<tr>
<td>Children with AcCMV without congenital SNHL (n=83)</td>
<td>2 mo. (4 days-11 mo.)</td>
<td>17 yrs. (23 days-18 yrs.)</td>
<td>7 (1-16)</td>
</tr>
<tr>
<td>Children with AcCMV and congenital SNHL (n=9)</td>
<td>2 mo. (28 days-10 mo.)</td>
<td>17 yrs. (13-18 yrs.)</td>
<td>11 (7-17)</td>
</tr>
</tbody>
</table>
Congenital SNHL among Children with AcCMV (n=92)

- 92 Newborns
  - 23 (25%) with first ABR click response threshold >25dB
    - 9 (39%) categorized as having congenital SNHL
      - 1 (11%) Bilateral loss
      - 8 (89%) Unilateral loss
    - 14 (61%) had normal hearing at follow-up
  - 69 (75%) with normal hearing at first evaluation
Delayed-Onset SNHL among Children with AcCMV with Unilateral Congenital SNHL (n=8)

8 children with unilateral congenital SNHL

6 (75%) subsequently developed delayed-onset SNHL in the contra-lateral ear

2 (25%) remained unilateral SNHL
Delayed-Onset SNHL among Children with AcCMV with Normal Hearing at Birth (n=83)

83 without congenital SNHL

11 (14%) Delayed-onset SNHL

67 (81%) Normal hearing at end of follow-up

6 lost to follow-up after first evaluation
### SNHL among children with AcCMV Infection and Controls

<table>
<thead>
<tr>
<th>Probability (%) (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td><strong>Controls</strong></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>25 (17-36)</td>
<td>8 (3-22)</td>
</tr>
<tr>
<td>Children with no SNHL at age 5 years</td>
<td>13 (7-25)</td>
<td>8 (3-22)</td>
</tr>
</tbody>
</table>

- The risk of SNHL diagnosed at any age was greater for cases than controls.
- For children with no SNHL at age 5 years, the risk of subsequently developing SNHL was not significantly greater for cases than controls.
### Delayed-onset SNHL among Children with AcCMV with and without Congenital SNHL

<table>
<thead>
<tr>
<th>Initial hearing status</th>
<th>Probability of delayed-onset SNHL (%) (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital unilateral loss</td>
<td>75 (44-96)</td>
<td>6.9 (2.5-19.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No congenital loss</td>
<td>16 (9-28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- The risk of delayed-onset SNHL was greater for children with congenital unilateral SNHL than those without.
Hearing Threshold Variability among Children with AcCMV with SNHL (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Fluctuating progressive</td>
<td>9</td>
</tr>
<tr>
<td>Progressive</td>
<td>6</td>
</tr>
<tr>
<td>Stable</td>
<td>7</td>
</tr>
<tr>
<td>Fluctuating non-progressive</td>
<td>1</td>
</tr>
<tr>
<td>Insufficient data**</td>
<td>3</td>
</tr>
</tbody>
</table>

11 (55%) children had fluctuating progressive or progressive HL in one or both ears

* Children were counted twice in case of different change in SNHL over time for each ear

**Insufficient data because SNHL was diagnosed in the last exam
Change in Degree of SNHL Over Time among Children with AcCMV with SNHL

<table>
<thead>
<tr>
<th>SNHL over time</th>
<th>Bilateral SNHL Ears (n)</th>
<th>Bilateral SNHL Children* (n)</th>
<th>Unilateral SNHL Children (n)</th>
<th>All children with SNHL n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Fluctuating progressive</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>Stable</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Fluctuating non-progressive</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Insufficient data**</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>9</td>
<td>11</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

* Three children were counted twice because they had progressive SNHL in one ear and stable or fluctuating progressive SNHL in the other ear.

**Insufficient data because SNHL was diagnosed in the last exam.
Cumulative Number and Proportion of Children with AcCMV with Bilateral and Unilateral SNHL by Age (n=20)

- Unilateral loss
- Bilateral loss

Age group (years) | Unilateral loss | Bilateral loss
--- | --- | ---
0-0.25 | 100% | 18%
0.25-1 | 82% | 27%
2-4 | 73% | 31%
5-7 | 69% | 31%
8-10 | 53% | 47%
11-14 | 63% | 37%
15-18 | 50% | 50%
Severity of AcCMV SNHL in the Worse Ear by Age Group (n=20)

12 (60%) children with moderate to profound SNHL at end of follow-up
Severity of AcCMV SNHL in the Better Ear by Age Group (n=20)

2 children with moderately severe to profound bilateral SNHL by age 2-4 yrs
4 children with moderate to profound bilateral SNHL
Degree of SNHL among Children with Asymptomatic cCMV Infection by Age

- **Worse ear**
  - 3 months: 1/6 (17%) with profound loss
  - End of follow-up: 9/20 (45%) with profound loss

- **Better ear**
  - 3 months: all 6 normal (unilateral loss)
  - 1 year: 2/11 had mild loss, other 9 normal hearing
  - 2-4 years: 1/11 progressed from mild to profound loss +
    1 diagnosed with moderately severe loss
    - 2% (95% CI: 1-9%) had bilateral SNHL ≥ 70 dB
  - At end of follow-up: 2 additional cases progressed to moderate loss (one at age 6 years and other at age 18 years)
    - Overall, 4% (95%CI: 1-11%) had bilateral moderate to profound SNHL by 6 years
Prevalence of SNHL among children born with AcCMV and controls

[Kaplan-Meier curves compare probability of SNHL between AcCMV and Controls P<0.05]
Conclusions

- An estimated 25% of children with AcCMV develop SNHL
  - ~2% will have bilateral SNHL ≥ 70dB by age 4 years
  - ~4% will have bilateral SNHL ≥ 40dB by age 6 years

- Greater risk of delayed-onset loss
  - Observed among children AcCMV with congenital loss than without congenital loss
  - Not significant among comparing children with AcCMV and controls with no hearing loss by age 5 years

- Risk of SNHL progression continues at least until 18 years of age for some AcCMV
Limitations

- Sample size was small to detect a significant small difference in probability of SNHL diagnosed at age >5 years between children with asymptomatic cCMV infection and controls.

- Fewer controls than cases enrolled and followed.

- No data on excessive exposure to harmful noise.

- Proportion of fluctuating progressive SNHL could have been underestimated because some children had fewer exams.
The Houston Congenital CMV Longitudinal Study and my CMV efforts have been supported for over 30 years by these grants and contributions:

- Baylor College of Medicine CMV Research Fund Donors
- The Woman’s Hospital of Texas Research Foundation
- General Clinic Research Center at Texas Children’s Hospital
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- Deafness Foundation, Houston, TX
- Vale Ashe Foundation, Houston, TX
- Maddie’s Mission, Katy, TX
- Naymola Charitable Foundation, Beaumont, TX
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  - CDC Cooperative Agreement FOA IP 10-006
  - CDC Contract No. 0009280120/8454RU92
  - CDC Contract No. 0009184031/8403R491
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