18-year Audiologic Follow-up of Children with Asymptomatic Congenital Cytomegalovirus Infection (AcCMV)

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Marily Flores, Peggy Blum, Jerry Miller, A. Chantal Caviness, Stephanie R. Bialek, Scott Grosse, Gail Demmler-Harrison for the Houston Congenital CMV Longitudinal Study

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Background

- An estimated 28,000 infants are born with congenital cytomegalovirus (cCMV) infection every year
  - ~25,000 (90%) are asymptomatic at birth
- Goderis et al, 2014 – Systematic review of many studies found:
  - ~10% children with cCMV infection that is asymptomatic at birth will have sensorineural hearing loss (SNHL), among which
    - ~10% delayed-onset
    - ~20% progressive
    - ~40% bilateral severe to profound degree

Limitations

- Studies had median follow-up range of 18 mo. to 7 yrs. It is rare children are being followed up to adolescence
- Many studies aggregated both ears into one and may report only the better ear:
  - In bilateral asymmetrical hearing, only the better ear may be used to quantify magnitude and impact of CMV on hearing
  - In unilateral hearing loss the normal hearing ear may be overlooked
- Thus, underestimate of delayed-onset and progressive SNHL and overestimate of severity are likely
What if We Follow these Children Longer?

With a cohort of asymptomatic cCMV identified through newborn screening where some have been followed for up to 18 years of age, I like to show you:

- The point prevalence of SNHL
- and their hearing loss characteristics
The Houston Congenital CMV Longitudinal Study

- During 1982-1992, newborns with cCMV infection were identified through hospital-based screening
  - Urine culture was obtained within 3 days of life
  - Newborns with asymptomatic cCMV infection: i.e. no CMV-related symptoms at birth (no purpura/petechiae, jaundice, hepatosplenomegaly, microcephaly, elevated liver enzymes, or thrombocytopenia)
- Long term follow-up included serial age-appropriate audiological evaluations
- Follow-up through 18 years of age for some
How do we Classify Hearing Loss?  
Congenital vs Late Onset

- **Congenital SNHL** (sensorineural hearing loss)
  - SNHL at the first ABR and persisted in subsequent follow-evaluations in the same ear
    - **Definite congenital**: first ABR done within 3mo. of life
    - **Presumed**: first ABR done between 3-12 mo.

- **Delayed-onset SNHL**
  - SNHL diagnosed in a previously normal hearing ear, or
  - SNHL diagnosed after 1 year of age when that was the first audiological evaluation
Definitions

- **SNHL**
  - *Sustained* thresholds $\geq 25$ dB on ABR click, any individual frequency, or 4PTA (average of 0.5-1,2,4 kHz), in the absence of transient middle ear disorder

- **Other classifications used:**
  - Unilateral vs bilateral, severity (ASHA criteria) and hearing loss change pattern
Other Classifications of SNHL

- Hearing change criteria adapted from ASHA 1994:
  - ≥20 dB in any frequency
  - ≥10 dB in the 4 Pure Tone Average, or any other 2 or 3 adjacent frequencies
  - No-response has occurred at least in 3 adjacent frequencies that formerly has a response
Change in SNHL Degree Over Time

- Classifications used:
  - *Progressive*: overall hearing deterioration with no intermittent improvement
  - *Fluctuating progressive*: overall deterioration with intermittent improvements
  - *Fluctuating non-progressive*: no change between first and final test with intermittent improvements or deteriorations
  - *Stable*: no change and no intermittent improvement or deterioration

Why do we go to such length to define change?
Why do we go to such length to define Change and Fluctuation?

- It is known that hearing loss in CMV+ children fluctuates over time.

- For long follow-up period, depends on when one freezes the data to examine the hearing loss degree, one may see a stable hearing, an improvement or a deterioration.
Audiologic results of Children with Asymptomatic cCMV Infection where some children are followed up to 18yrs of age - the Houston cCMV Longitudinal Study

RESULTS
Cohort of Children with Asymptomatic cCMV Infection Identified through Newborn Screening

- **Follow-up**
  - 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,
    - 95% at age ≥ 9 yrs.
    (recall in Goderis review: a few studies followed up to 7 yrs.)
Congenital SNHL among Children with Asymptomatic cCMV Infection Identified through Newborn Screening

92 Newborns

9 (10%) Congenital SNHL

1 (11%) Bilateral

83 (90%) Normal hearing at first evaluation

8 (89%) Unilateral
Delayed-Onset SNHL among Children with Asymptomatic cCMV Infection with Normal Hearing at Birth (n=83)

- 83 with Normal hearing at first evaluation
  - 11 (14%) Delayed-onset SNHL
    - 3 (27%) Bilateral
    - 8 (73%) Unilateral
  - 67 (81%) Normal hearing at end of follow-up

6 lost to follow-up after first evaluation

58% dx between 5-10yrs
36% dx between 11-14yrs
9% dx between 15-18yrs
Delayed-Onset SNHL among Children with Asymptomatic cCMV Infection with Unilateral Congenital SNHL (n=8)

8 children with unilateral congenital SNHL

- 5 (63%) subsequently developed delayed-onset SNHL in the normal hearing ear
- 3 (37%) remained unilateral SNHL

4 dx after 4yrs of age and 1 dx at 6m of age
What is the Prevalence of SNHL among children with Asymptomatic cCMV Infection?

Putting the numbers back in the original total pool of asymptomatic children (N=92) for perspective after some were being followed for 18yrs.

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital SNHL, initially</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Delayed-onset SNHL, only</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Total with SNHL</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>
Proportion of Children with Asymptomatic cCMV Infection with Delayed-Onset SNHL

<table>
<thead>
<tr>
<th>Description</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>In total 20 children with SNHL after some were followed up to 18yrs of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed onset in initially normal hearing only (in this case unilateral hearing loss is excluded)</td>
<td>11/20</td>
<td>55</td>
</tr>
<tr>
<td>Any delayed-onset hearing loss (either in initial normal hearing and in the normal ear of unilateral HL)</td>
<td>16/20</td>
<td>80</td>
</tr>
<tr>
<td>Number of delayed-onset SNHL that occurred at or later than age 4yr (when children are followed up to 4yr. of age only)</td>
<td>14/20</td>
<td>70</td>
</tr>
</tbody>
</table>

Depends on the f/up period and how the children are classified affects the period prevalence prediction and our perception of the magnitude of the problem.
Fluctuation Pattern in Children with Asymptomatic cCMV Infection with SNHL (n=20)

<table>
<thead>
<tr>
<th>Change in SNHL over time</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>2</td>
</tr>
</tbody>
</table>

13 (65%) children had fluctuating progressive or progressive HL in one or both ears  
* Children were counted twice because one ear may fluctuate while the other may be stable  
**Insufficient data because SNHL was diagnosed in the last exam
## Comparison of Estimates from Goderis and Houston Study

<table>
<thead>
<tr>
<th>SNHL in children with AcCMV</th>
<th>Goderis, 2014</th>
<th>Houston Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>Unilateral</td>
<td>57%</td>
<td>55%</td>
</tr>
<tr>
<td>Severe to profound</td>
<td>78%</td>
<td>50%</td>
</tr>
<tr>
<td>Delayed-onset</td>
<td>9%</td>
<td>55-80%</td>
</tr>
<tr>
<td>Progressive</td>
<td>20%</td>
<td>30%*</td>
</tr>
<tr>
<td>Fluctuating</td>
<td>24%</td>
<td>50%*</td>
</tr>
</tbody>
</table>

*Either fluctuating progressive or non-progressive
The Risk of Losing even more hearing

Can we better predict which asymptomatic children will have delayed hearing loss?
## Risk of Delayed-Onset in Children with Asymptomatic cCMV Infection when some of them are Followed up to 18yr. of age

<table>
<thead>
<tr>
<th>Initial hearing status</th>
<th>Has Delayed-Onset SNHL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>In congenital unilateral SNHL</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>In bilateral normal hearing</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (19%)</td>
</tr>
</tbody>
</table>

Relative risk = 4.4 (95% CI: 2.0-9.4, p-value <0.01)

*Children with unilateral congenital SNHL had an increased risk of developing delayed-onset SNHL in the normal hearing ear compared to children with normal hearing bilaterally.*
4 children had moderate to profound bilateral SNHL
- 2 severe to profound bilateral SNHL by age 2-4 yrs → candidacy for cochlear implant
- An additional 8 children had moderate to profound unilateral SNHL
Summary

- SNHL prevalence: 22%
- Proportion delayed-onset SNHL diagnosed at age ≥ 4 yrs.: 70%
- Risk of delayed-onset SNHL in children with congenital unilateral SNHL as compared to children with normal hearing in the first 3 mo. of life: 4.4-fold
- Proportion with further SNHL deterioration: 65%
Conclusions

- Asymptomatic cCMV is associated with congenital and delayed-onset SNHL that may manifest and progress through adolescence.

- Ongoing long-term audiological follow-up is needed for providing timely interventions and understanding the burden of CMV-related SNHL.
THANK YOU

Questions?
### Age at First and Last Evaluation and Number of Evaluations

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (range)</th>
<th>Number of evaluations per subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at first audiological evaluation</td>
<td>Age at last audiological evaluation</td>
</tr>
<tr>
<td>All children with AcCMV (n=92)</td>
<td>2 mo.</td>
<td>17 yrs.</td>
</tr>
<tr>
<td></td>
<td>(4 days-11.5 mo.)</td>
<td>(23 days-18 yrs.)</td>
</tr>
<tr>
<td>Children with AcCMV without congenital SNHL (n=83)</td>
<td>2 mo.</td>
<td>17 yrs.</td>
</tr>
<tr>
<td></td>
<td>(4 days-11 mo.)</td>
<td>(23 days-18 yrs.)</td>
</tr>
<tr>
<td>Children with AcCMV and congenital SNHL (n=9)</td>
<td>2 mo.</td>
<td>17 yrs.</td>
</tr>
<tr>
<td></td>
<td>(28 days-10 mo.)</td>
<td>(13-18 yrs.)</td>
</tr>
</tbody>
</table>
Long-Term Hearing Outcomes

92 newborns with AcCMV identified by screening

83 (90%) normal hearing at birth

- 67 (81%) normal hearing up to last evaluation
- 8 (10%) delayed-onset unilateral SNHL
- 6 (7%) drop-outs after 1st ABR

- Age at 1st diagnosis:
  - 5-10 years: 5 (45%)
  - 11-14 years: 4 (36%)
  - 15-18 years: 1 (9%)

8 (9%) congenital unilateral SNHL

3 (4%) delayed-onset bilateral SNHL

5 (63%) delayed-onset SNHL contra-lateral ear

1 (1%) congenital bilateral SNHL

8 (9%) congenital unilateral SNHL

Proportion with bilateral SNHL

<table>
<thead>
<tr>
<th>Description</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis of congenital SNHL</td>
<td>1/9</td>
<td>10</td>
</tr>
<tr>
<td>At last evaluation</td>
<td>9/20</td>
<td>45</td>
</tr>
</tbody>
</table>
Change in Degree of SNHL Over Time among Children with Asymptomatic cCMV Infection with SNHL

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