Results of a Targeted Screening Program for Congenital Cytomegalovirus (cCMV) Infection in Montréal, Québec

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Targeted Screening

• Universal vs. targeted screening for cCMV infection is a subject of considerable debate

• Identifying risk factors that allow for targeted screening cCMV patients would diminish the costs and potentials risk associated with universal screening – identifying those who need treatment

• A number of centers have started targeted CMV screening of infants who fail newborn hearing screen

• Other targeted groups considered: Infants of HIV infected mothers, infants admitted to NICU
The objective of this study is to describe the experience with targeted CMV screening through infant newborn hearing program, at CHU Sainte-Justine, Montreal, Quebec.

- **Phase I:** 2008-2011
- **Phase II:** 2014-2018
CHU Sainte-Justine

450 bed Maternal-Child Health Center
Montréal, Québec

3500 births/year
65 bed NICU
Tertiary care for premature babies and neonatal surgery
Beginning in 2008, the PQDSN program was meant to diagnose and manage:

- **Moderate or profound bilateral hearing loss:**
  - $\geq 40$ dBHL
  - Average thresholds at frequencies: 500-1000-2000-4000 Hz

- **Bilateral ANSD (auditory neuropathy spectrum disorder)** in babies presenting at least one hearing risk factor
As part of the UNHS program, all infants were tested using a combined protocol of

- Automated distortion product otoacoustic emissions (DPOAE-A)
- Automated auditory brainstem response (A-ABR)
Risk factors for hearing loss

- Family history of hearing loss
- Congenital infection suspected or confirmed
- Craniofacial anomaly
- Genetic syndrome associated with hearing loss
- Hyperbilirubinemia
- Very low birth weight (VLBW) less than 1500g
- Prematurity (less than 29 weeks of gestation)
- Respiratory disorders
- Neurology disorders
- Excessive doses of ototoxic drugs
- Confirmed bacterial or viral meningitis
- Anotia, microtia, atresi (one or both ears)
- Extended stay in NICU (reached the corrected age of 3 months)
UNHS protocol
Newborn WITHOUT risk factors

End of programme
Succeed
DPOAE-A
Referred

CMV Screening

2 weeks later
In the outpatient clinic

A-ABR
Referred

End of programme
Succeed
A-ABR
Referred

Comprehensive audiological evaluation
UNHS protocol
Newborn WITH risk factors

End of programme  Succeed  A-ABR

CMV screening

Referred

2 weeks later
In the outpatient clinic

End of programme  Succeed  A-ABR  Referred

Comprehensive audiological evaluation

NICU
20% of Births at CHUSJ
METHODS

• Retrospective analysis of UNHS results related to CMV screening results

• The data for the current study were drawn from 3 sources
  • CHU Ste-Justine UNHS database
  • CHU Ste-Justine Virology Laboratory
  • CHU Ste-Justine CMIS HIV database

Phase 1: 2008-2011, Urine PCR
Phase 2: 2013-2018, Saliva PCR
UNHS from 2008 to 2011

11363 Newborns

NICU n=2468
- Not tested 264
- tested n=2204 (89.3%)
  - Succeed n=1815
  - Referred n=389 (17.6%)
    - 2nd tested n=299
      - Referred n=82
    - Hearing loss n=34 (1.5%)

Newborn Nursery n=8895
- Not tested 16
- tested n=8879 (99.8%)
  - Succeed n=8559
  - Referred n=320 (3.6%)
    - 2nd tested n=295
      - Referred n=30
    - Hearing loss n=8 (0.1%)

1% comprehensive audiological evaluation
UNHS from 2008 to 2011

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- Not tested 264
  - tested n=2204 89.3%
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      - Referred n=389
        - 2nd tested n=299
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        - 2nd tested n=295
          - Referred n=30
            - Hearing loss n=8
CMV urine testing (shell vial) in the nursery

n=226 tested for CMV
(320 Referred)

- Unilatérale 83%
- Bilatérale 17%

75.2% CMV screened
24.8% CMV unscreened

Newborn urine bag collection
CMV testing in children with hearing loss (n=42)
PHASE I 2008-2011

- Newborn nursery n=8:
  - CMV positive = 0
  - CMV negative = 3
  - CMV unscreened = 5

- NICU n=34:
  - CMV positive = 3 (8.8%)
  - CMV negative = 11
  - CMV unscreened = 20

Medoro et al. “Targeted” Screening for Cytomegalovirus (CMV)-Related Hearing Loss: It’s Time for Universal CMV Screening in the NICU!, Abstract 2326, ID Week 2017
Validation of CMV Screening from Saliva with in house CMV PCR

Comparison of 56 patients tested by CMV urine culture and CMV PCR on saliva (2012)

<table>
<thead>
<tr>
<th></th>
<th>Urine +</th>
<th>Urine -</th>
</tr>
</thead>
<tbody>
<tr>
<td>saliva +</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Saliva -</td>
<td>0</td>
<td>43</td>
</tr>
</tbody>
</table>

Sensitivity: 100%
Specificity: 91.5%

Decision to screen with CMV PCR on saliva but confirm with CMV PCR on urine
Revised and upgraded targeted screening Program for cCMV in the Newborn Nursery

2014-2018: Phase II, Saliva testing by PCR for

<table>
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<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>All newborns who did not pass their hearing test</td>
</tr>
<tr>
<td>All newborns of HIV infected mothers</td>
</tr>
<tr>
<td>All newborns symptoms suggestive of cCMV (paediatrician's judgement) ex: IUGR, thrombocytopenia, hepatitis, cholestasis, hepatosplenomegaly) or of mothers with confirmed or suspected primary CMV infection in pregnancy</td>
</tr>
</tbody>
</table>
UNHS Targeted cCMV Screening from 2014 to 2018

Nursery 
n=12189

CMV risk factors or symptoms n= 455

Succeed n = 11198

Referred n=536  4,5%

CMV tested n= 484

2nd tested n= 507

Referred n = 40  0,3%

Hearing loss n= 23  0,2%

CMV positive n = 0

CMV positive  n=3  0,025%
cCMV Screening (newborns with identified with risk factors) 2014 to 2018

Nursery
n=12189

CMV Risk Factors/symptoms n= 455

HIV infected mother n=130

Sx or Risk factors for cCMV n= 325

tested n= 116

tested n= 294

2.6% CMV positive  n=3

6.8% CMV positive  n=20
RESULTS

• Using these combined methods, a total of 0.21% of newborns enrolled in the targeted screening program tested positive for cCMV infection

• Incidence of cCMV is unknown in our population but we expect 0.5 to 1% as other North American metropolitan populations…

<table>
<thead>
<tr>
<th>Symptomatic or risk factor</th>
<th>HIV exposed</th>
<th>UNHS only</th>
</tr>
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<tbody>
<tr>
<td>% Positive for CMV among those screened</td>
<td>6.8%</td>
<td>2.6%</td>
</tr>
<tr>
<td>% of overall cohort</td>
<td>0.17%</td>
<td>0.025%</td>
</tr>
</tbody>
</table>
From the laboratory perspective...

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Urine</th>
<th>Saliva</th>
<th>Patient Age (average in days)</th>
<th>Positive Patients</th>
<th>Shell Vial</th>
<th>PCR</th>
<th>Tube Culture</th>
<th>Low Positive CMV PCR in Saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>194</td>
<td>137</td>
<td>30</td>
<td>5,6</td>
<td>4</td>
<td>212</td>
<td>13</td>
<td>183</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>297</td>
<td>158</td>
<td>219</td>
<td>4,1</td>
<td>4</td>
<td>340</td>
<td>140</td>
<td>215</td>
<td>1</td>
</tr>
<tr>
<td>2014</td>
<td>340</td>
<td>122</td>
<td>254</td>
<td>3,6</td>
<td>8</td>
<td>350</td>
<td>180</td>
<td>212</td>
<td>1</td>
</tr>
<tr>
<td>2015</td>
<td>334</td>
<td>148</td>
<td>221</td>
<td>3,3</td>
<td>3</td>
<td>25</td>
<td>352</td>
<td>340</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>375</td>
<td>129</td>
<td>270</td>
<td>3,1</td>
<td>11</td>
<td>2</td>
<td>391</td>
<td>381</td>
<td>0</td>
</tr>
<tr>
<td>2017</td>
<td>423</td>
<td>127</td>
<td>323</td>
<td>2,7</td>
<td>12</td>
<td>0</td>
<td>446</td>
<td>443</td>
<td>3</td>
</tr>
</tbody>
</table>

- More patients are tested every year in the targeted screening program
- Same number of patients are tested in the NICU every year
- Patient age at testing has gone down annually
- Approximately 13% false positive in saliva

**cCMV Targeted Screening**

**NICU (Mainly symptomatic testing)**
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sample Size (Excluding NICU/CMV)</th>
<th>Referred (1st) (%)</th>
<th>Confirmed HL (SNHL and Mixte)</th>
<th>CMV Test (Mixte)</th>
<th>CMV Test (%)</th>
<th>Confirmed hearing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renaud et al. 2018</td>
<td>Québec</td>
<td>11734 births</td>
<td>536 (4,6%)</td>
<td>23</td>
<td>484 mixing saliva</td>
<td>0%</td>
<td>0,37%</td>
</tr>
<tr>
<td>Diener et al. 2017</td>
<td>Utah</td>
<td>103868 births (NICU?)</td>
<td>509 (0,4%)</td>
<td>104</td>
<td>314 mixing saliva</td>
<td>5,7%</td>
<td>2,75%</td>
</tr>
<tr>
<td>Roth et al. 2017</td>
<td>Israel</td>
<td>19830 births (including NICU)</td>
<td>200 (1%)</td>
<td>36</td>
<td>178 mixing saliva</td>
<td>8,3%</td>
<td>2%</td>
</tr>
<tr>
<td>Vancor et al. 2018</td>
<td>Connecticut</td>
<td>10964 births (NICU?)</td>
<td>171 (1,6%)</td>
<td>22</td>
<td>171 mixing saliva</td>
<td>4,5%</td>
<td>1,8%</td>
</tr>
<tr>
<td>Stehel et al. 2008</td>
<td>Texas</td>
<td>79047 births</td>
<td>572 (0,7%)</td>
<td>256</td>
<td>483 urine</td>
<td>6,3%</td>
<td>4,2%</td>
</tr>
<tr>
<td>Kadambari et al. 2015</td>
<td>UK</td>
<td>10385 births (NICU?)</td>
<td>349 (3,4%)</td>
<td>203</td>
<td>24 mixing saliva</td>
<td>0,6%</td>
<td>0,019%</td>
</tr>
</tbody>
</table>
Using these same criteria:
- HIV infected mothers
- UNHS
- Clinical

Identified 50 cCMV cases
= 0.06% of the cohort

CIME cohort: We identified 0.21% of the cohort with cCMV

Difference in criteria (clinical thresholds? Or difference in incidence?)

6.3% of Confirmed
4.2% of Referred
0.034% of cohort
8/24 normal hearing
Future directions

Is the UNHS a good targeted population for cCMV screening?

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<td>0.62%</td>
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<td>% of overall cohort</td>
<td>0.17%</td>
<td>0.025%</td>
<td>0.017%</td>
</tr>
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Improving targeted screening – beyond the hearing program

• Define additional risk factors for cCMV infection (other infants to target):
  ➢ All infants of immunocompromised mothers
  ➢ With data from local epidemiology

• Enhance nursery identification/physician awareness of symptoms for screening

• Consider other at risk groups to targeted (NICU)
Acknowledgements

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**Dr. C. Renaud