Expert opinion on clinical symptoms, management and treatment of infants with congenital cytomegalovirus infection

J. Gunkel, J. Nijman, M.A. Maciolek-Verboon, T.F.W. Wolfs, L.S. de Vries
Financial disclosure

Dr. J. Gunkel was financially supported by the Dutch Phelps Foundation (http://phelps-stichting.nl/).
Congenital cytomegalovirus (cCMV) infection

- Global birth prevalence\(^1\): 0.7%
- **Symptomatic**\(^1\): ± 12.7%
  - 5-10% mortality rate
  - 40-58% permanent sequelae
- **Asymptomatic**\(^1\): ± 87.3%
  - 13.5% permanent sequelae

- **The Netherlands (NL)**\(^2\)
  - 0.54%  
  - 1000 cCMV infected children/ year
  - 12.7%  
  - 127 symptomatic infants
  - 87.3%  
  - 873 asymptomatic infants

\(^1\) Dollard et al. 2007; \(^2\) de Vries et al. 2011
Symptoms and disease burden

- Spectrum: mild/ transient ↔ overt/ life-threatening
- Non-genetic sensorineural hearing loss (SNHL)

**Central nervous system (CNS)**
- Microcephaly
- Intracranial calcifications
- Hearing loss

**Clinically apparent**
- Pneumonia
- Seizures

**Laboratory abnormalities**
- Small for gestation age
- Jaundice
- Hepato-splenomegaly
- Chorioretinitis
- Petechiae

(Smith et al. 2015; W. Britt 2008; Kimberlin et al. 2015)
cCMV and the brain

- Cranial ultrasound (cUS)
- Magnetic resonance imaging (MRI)

Lenticulostriate vasculopathy (LSV)

Polymicrogyria

Cerebellar hypoplasia

Advancements & limitations

• Natural history, epidemiology, management

• Treatment: (Val)ganciclovir for symptomatic infants (not entirely effective)
  – Non-medicinal: hearing aides/ therapy

• Prevention
  – Hygiene measures: effective
  – Vaccination: not yet available, nor entirely effective
  – CMV-hyperimmune globulins: conflicting results

• Awareness
  – Lacking amongst health care providers & pregnant women

(Kimberlin et al. 2015; Revello et al. 2015; Rieder & Steininger, 20014; Revello et al. 2014)
Awareness & knowledge of cCMV in NL

Medical doctors

<table>
<thead>
<tr>
<th>Knowledge concerning</th>
<th>Total number of respondents (n = 246) (%)</th>
<th>Number of pediatricians (n = 85) (%)</th>
<th>Number of obstetricians and gynecologists (n = 18) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>True answers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>50 (20.3)</td>
<td>27 (31.8)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>71 (28.9)</td>
<td>45 (52.9)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>109 (44.3)</td>
<td>57 (67.1)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>138 (56.1)</td>
<td>73 (85.0)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>IUGR</td>
<td>146 (59.3)</td>
<td>61 (71.8)</td>
<td>16 (88.9)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>138 (56.1)</td>
<td>67 (78.8)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>Seizures</td>
<td>68 (27.8)</td>
<td>40 (47.1)</td>
<td>6 (33.3)</td>
</tr>
</tbody>
</table>

Midwives

Number of consultations in which preventive information for toxoplasmosis, listeriosis or CMV were mentioned by midwives (N = 172 consultations).

<table>
<thead>
<tr>
<th>Items</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Not eating raw or undercooked meat</td>
<td>135 (78.5)</td>
</tr>
</tbody>
</table>
Dutch cCMV Surveillance Study

- January 2013 – December 2015
- Surveillance amongst Dutch pediatricians
- Passive registration with parental consent
  - 3 questionnaires
    - maternal/gestational, neonatal characteristics, neurodevelopment
- 55 registrations made; 48 (87%) included
- Expected number of registrations: ±390 infants
  - Registered: 12%
Aims of our study

• Evaluate standard practice in identification and current practices in management of infants with cCMV infection
  – Health care professionals dealing with cCMV infection
Method – Questionnaire study

- Online questionnaire
- September 2014 – July 2015

Addition of 5 extra questions:
- Maternal & infant screening
- Symptomatology
- Diagnostics
- Management
- Follow-up

21 questions

37 European neonatal centers

26 questions

Effective Perinatal Intensive Care (EPICE)

ESPID congress 2014 cCMV meeting
Questionnaire study

Results
Maternal screening

• 63 responses (63/111; 57%)
  • 19 countries; majority neonatologist (n=40; 64%)

1. Are pregnant women screened for CMV-serostatus during pregnancy?

   - 27% Yes
   - 68% No, only upon clinical indication
   - 3% Not sure
   - 2% Unanswered

2. If yes, when are pregnant women screened during pregnancy?

   - Unanswered: 29%
   - Every month until seroconversion: 24%
   - 1T+3T: 6%
   - 1T+2T: 12%
   - 1T: 29%
4. Are infants screened for cCMV infection at your hospital?

- 89% No, only upon clinical indication
- 5% Yes
- 6% Unanswered
5. Do you think it’s important to screen for cCMV infection?

- 0% (Unanswered)
- 43% (No)
- 13% (Prior & during)
- 10% (Prior, during & after)
- 6% (During & after)
- 6% (After)
- 5% (Prior)
Infant diagnostics

6. With what materials are infants diagnosed/screened?

- **Urine**: 75% Yes, 16% No, 9% Not sure, 1% Unanswered
- **Saliva**: 84% Yes, 16% No, 1% Not sure, 0% Unanswered
- **Blood**: 54% Yes, 46% No, 0% Not sure, 0% Unanswered
- **DBS card**: 27% Yes, 73% No, 0% Not sure, 0% Unanswered
Infant symptomatology

7. What symptoms would urge you to test for cCMV infection?

![Bar chart showing percentages of symptoms associated with cCMV infection. The symptoms include:
- Thrombocytopenia or anemia: 83%
- HSM or increase in LE: 87%
- Conjg. hyperbilirubinemia: 71%
- Ophthalmological disorders: 79%
- Hearing loss: 84%
- Neurological disorders: 64%
- Neuro-imaging abnormalities: 78%
- Other: 18%]

Results
Infant symptomatology

Number of symptoms chosen per respondent
(total 9 CMV-associated symptoms to choose from)
**Infant neuro-imaging**

8. Do infants with a proven cCMV infection get a standard cUS?
   - 3%: yes, but only in symptomatic infants
   - **91%: yes, in both symptomatic & asymptomatic infants**
   - 3%: no
   - 3%: not sure

9. Standard MRI/ CT scan during admission period?
Infant neuro-imaging

10. Do you think infants with cCMV should get a standard cUS/ MRI/ CT?

Results:
- Yes: 89%
- No: 3%
- Not sure: Frequencies not shown in the diagram
11. How important is neuro-imaging in the management of cCMV infected infants?

- 68% Very important
- 27% Moderately important
- 5% Unanswered
Antiviral treatment

12. Are antivirals used in the management of cCMV infected infants at your hospital?

Duration: **6 weeks (52%); 6 months (13%); 12 months (2%); not sure (22%); other (11%)**
Hearing examination

13. Are symptomatic/ asymptomatic infants followed-up audiologically?

Timing: during 1st admission, 3 months, 6 months, 12 months, yearly until 6 years = 32%
**Discussion**

**Main learning points:**

- Awareness among health care providers is lacking
  - Symptom identification
  - Management
  - Follow-up

- Consensus in standard practice lacking

- Large portion of symptomatic infants not recognized
  - 35% choose all symptoms characteristic of cCMV infection
  - Asymptomatic infants

- Are we identifying all infants that may benefit from intervention?
Discussion

- cCMV identification is a problem
  - Symptom recognition
  - Symptoms not pathognomonic for CMV

- Solution: **universal screening**

- **Benefits of infant screening:**
  1. Identification of symptomatic infants that may benefit from antiviral therapy
    1. Prevention of hearing deterioration
  2. Early identification of (late-onset) hearing loss
    1. Promote normal speech & language development
Discussion

• Enrollment into systematic long-term follow-up studies
  – Epidemiology
  – Disease burden

• **Targeted- or universal screening?**

• Without universal screening, identification is solely based on correct symptom identification.
Conclusion

• cCMV is a public health issue of major concern

• Continue efforts to spread awareness & educate

• Research on national or localized universal screening programs needed to explore its feasibility & effectiveness
  – No more registries

• Development of international guideline regarding recommendations in identification & management

“Knowing is not enough; we must apply.
Willing is not enough; we must do.”
- Goethe -
Thank you

Postnatal and congenital CMV infection research group
Wilhelmina Children’s Hospital, Utrecht, The Netherlands

Prof. Linda S. de Vries, MD PhD
Neonatologist, Professor in neonatal neuro-imaging

Tom F.W. Wolfs, MD PhD
Pediatrician, pediatric infectious diseases

Joppe Nijman, MD PhD
Post-doc neonatology, pediatrics resident

Malgosia A. Verboon-Maciolek, MD PhD
Neonatologist, neonatal & viral infectious diseases
Julia Gunkel:  j.gunkel@umcutrecht.nl

Utrecht, The Netherlands