Screening for Congenital CMV Infection

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Overview

Definition

Criteria

Potential benefits

Comparison with other conditions

How screen?
  - Universal
  - Selective

What specimen?
  - DBS
  - Saliva
Definition of Screening

The systematic application of a test to identify asymptomatic individuals at risk of a specific disorder in order to prompt further investigation or preventative action.

Benefits must outweigh harms.

Does CMV meet criteria for screening?

Common problem ✓
Serious problem ✓
Natural history defined ✓
Confirmatory tests ✓

Effectiveness of screening?
Acceptability of screening?
  • Health care providers
  • parents

Cost-effective?

Is there definitive evidence that screening leads to improved outcome?

If no, consider:

- Is the natural history defined?
- Is there a valid screening test?
- Is the clinical validity defined?
  - Sensitivity and specificity
- What is the clinical utility?
  - Benefits
  - Harms
- Are screening, diagnosis and treatment cost-effective?
Potential benefits

- RCT of ganciclovir ✓
  - Recruited symptomatics, CNS
  - Prevents future disease
    - Pre-emptive therapy
- RCT of valganciclovir ✓
  - Recruited symptomatics
  - VGCV well tolerated
- Now consider RCT in asymptomatics?
Consider a RCT

Asymptomatics

Compare VGCV with controls
  • Screening
  • RCT

Placebo

6 weeks?

6 months or other?
Figure 2. Cytomegalovirus DNA Viral Load in Whole Blood in Participants Receiving the Study Therapy. Participants with a viral load of less than 100 were assessed as having a viral load of 10 (i.e., 1.0 in the graph). P values are for the between-group comparisons at the respective time points.
Comparison with other conditions

![Bar chart comparing the annual number of damaged babies with various conditions](chart)

- **Screening Programmes**
  - CRS: 10
  - HIV: 200
  - SB: 3000
  - DS: 4000

- **Antenatal Advice**
  - Toxo: 1000
  - FAS: 5000

- **Neither**
  - CMV: 7670

Annual Cases in USA of 27 Conditions now Screened for in Most States (total 6,618 cases)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic acids</td>
<td>8,000</td>
</tr>
<tr>
<td>Amino acids</td>
<td>6,000</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>4,000</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>2,000</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>40,000</td>
</tr>
<tr>
<td>Others</td>
<td>355</td>
</tr>
</tbody>
</table>

DBS Screening

Rapid DEAFF of saliva

PCR run with:

- Single primer set
- Dual primer set

11,422 neonates single primer:
- 17/60 (28%) sensitivity

9,026 neonates dual primer:
- 11/32 (34%) sensitivity

Boppana SB. JAMA, 303, 1375, 2010.
Schematic Diagram of Single Tube Nested PCR

Outer 1 → 373bp → Outer 2

Inner 1 → CMV UL123 → Inner 2

Probe → 291bpp

(not to scale)

Saliva PCR Screening

Rapid DEAFF of saliva

PCR of saliva without DNA extraction:

- Transport medium, 4°C
- Dried swab, RT

17,622 neonates tested liquid PCR
- 85/85 (100%) sensitivity
- 99.9% specificity

17,327 neonates tested dry PCR
- 74/76 (97%) sensitivity
- 99.9% specificity

Boppana SB. NEJM, 364, 2111, 2011.
DBS vs Saliva

Shared features

- Need PCR at screening centres

DBS

- Fits onto existing screening programme
- May be able to pick up many cases at risk of disease
- Smaller number of cases to be followed

Saliva

- Requires parallel system for collection and delivery
- Will identify more cases, many of which not at risk of disease
## CMV-related disability

<table>
<thead>
<tr>
<th>Annual Number of:</th>
<th>Australia (population ~22 million)</th>
<th>England &amp; Wales (population ~50 million)</th>
<th>USA (population ~307 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Births</td>
<td>296,600</td>
<td>709,000</td>
<td>4,248,000</td>
</tr>
<tr>
<td>Congenital CMV infections (0.6%)</td>
<td>1,780</td>
<td>4,254</td>
<td>25,488</td>
</tr>
<tr>
<td>Symptomatic at birth (12.8%)</td>
<td>228</td>
<td>544</td>
<td>3,262</td>
</tr>
<tr>
<td>Develop disability (50%)</td>
<td>114</td>
<td>272</td>
<td>1,631</td>
</tr>
<tr>
<td>Asymptomatic at birth (87.2%)</td>
<td>1,552</td>
<td>3,710</td>
<td>22,226</td>
</tr>
<tr>
<td>Develop disability (13.5%)</td>
<td>210</td>
<td>501</td>
<td>3,001</td>
</tr>
<tr>
<td>Total CMV-related disabilities</td>
<td>324</td>
<td>773</td>
<td>4,632</td>
</tr>
</tbody>
</table>
### Symptoms at Birth

<table>
<thead>
<tr>
<th>Symptomatic at Birth</th>
<th>No Benefit</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed clinically</td>
<td>815</td>
<td></td>
</tr>
<tr>
<td>Not diagnosed but no HL</td>
<td>1,504</td>
<td></td>
</tr>
<tr>
<td>Not diagnosed but HL</td>
<td>943</td>
<td></td>
</tr>
</tbody>
</table>

### Asymptomatic at Birth

<table>
<thead>
<tr>
<th>Asymptomatic at Birth</th>
<th>No Benefit</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HL</td>
<td>19,514</td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>2,712</td>
<td></td>
</tr>
</tbody>
</table>
Selective Screening with Written Consent

Newborns with “no clear responses” on hearing screen

- Saliva and urine requested for PCR
- Baseline and 3 month maternal anxiety measured

411 recruited

99% returned a sample

- 99% saliva
- 50% urine

6 cases congenital CMV detected

- All within 23 days of birth
- 5/6 assessed for VGCV within 31 days

Anxiety not increased in mothers
Selective Screening as a Routine

Newborns with “no clear responses” on hearing screen

• Hearing screeners trained to collect saliva

203/255 eligible newborns had swab taken

PCR results available within 31 days

Two cases of congenital CMV identified

• Reviewed by paediatrician within 10 days
Selective Screening: cost effectiveness

Costs of identification
- Screener time, swab, PCR, administration time

Costs for identified cases
- Paediatrician, laboratory tests, imaging, ophthalmology

Costs for treating some
- VGCV 6 weeks, monitoring bloods, paediatrician, ophthalmology

Costs for following asymptomatics
- Paediatrician, audiology

Total per treated case = £6,683
Total per improved hearing outcome = £14,202
Summary

Needs input on several fronts

- Laboratory assays
- Cohorts to evaluate assays
- Demonstration screening projects
  - Universal
  - Selective
- RCT of VGCV in asymptomatics
- Multidisciplinary interactions