Neonatal and infant HSV disease in Australia

Cheryl Jones, on behalf of APSU HSV investigators and contributors to the APSU

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The Children’s Hospital at Westmead
Overview Neonatal HSV

- Incidence, Presentation, Baby and maternal details
- Vertical transmission of HSV
- Risk Factors
- Investigations
- Treatment Prevention
Incidence presentation and maternal details
Neonatal HSV cases Australia 1997-2011

Reported incidence: 3.25 per 100,000 live births
Neonatal HSV in Australia 1997-2011

- Skin, Eye, Mouth: 46%
- Disseminated infection: 32%
- CNS: 22%
Vertical Transmission HSV
Mode of Vertical Transmission HSV

1. During pregnancy 5%

2. During delivery 85%

3. Postnally 10-15%

- Transplacental
- Ascending
- Close contact with mother
- Breast milk

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www.emorywomensprogram.org/images/QnA.jpg
Vertical Transmission of HSV

Most genital HSV infections are asymptomatic
(Primary or Recurrent)

PERINATAL
85%

70%
No knowledge of genital HSV disease

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Mode of Neonatal HSV Transmission
Australia 1997-2011

- Intrauterine 3%
- Perinatal ~49%
  Maternal genital HSV disease
- Postnatal- 20%
- Unknown/Not reported- 26%

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Risk Factors for Vertical Transmission Neonatal HSV
Risk factors for Vertical transmission

- Primary genital HSV disease: esp. late pregnancy
- HSV Serodiscordant partner
- Invasive Obstetric Procedures
  - Fetal scalp electrodes
  - Artificial ROM
  - Assisted delivery: ventouse/forceps
- Low maternal neutralising antibody levels to HSV
- Route of delivery: vaginal > c.section
- HSV serotype (HSV-1 > HSV-2)
- ? HIV co-infection

OR 6.8
Brown et al, 2003
Maternal HSV
Risk of vertical transmission

Primary genital HSV
- 30-50% if shedding at delivery

Recurrent genital HSV
- 3% if shedding at delivery
- ~0.04% if no shedding or symptoms

Risk of transmission greatest if HSV seroconversion has not occurred prior to onset of labour

If virus present in genital tract, Caesarean section reduces risk of transmission to newborn OR 0.14 (0.02 - 1.08)

Brown et al, 1991
Brown et al, 1997
Brown et al, JAMA 2003
HIV co-infection in pregnancy and vertical transmission of HSV?

HSV on HIV infection/ MTC transmission?
- Vertical transmission HIV 2-3 increased in HSV-2 seropositive mothers, Thai study *Bollen 2008*
- Not increased in US study *Chen 2008*

HIV on HSV vertical transmission?
- Not been fully defined.
- Prevalence of HSV-2 shedding in late pregnancy increased if HIV positive: 12.1% vs 1.7%
- Risk of HSV reactivation in African HIV-positive women is greater than in HIV-negative women, and the in pregnancy (8% vs 1–2%). *Hitti: 1997*
Serotype dependant risk of vertical transmission: Genital HSV-1 vs HSV-2

<table>
<thead>
<tr>
<th>Type HSV</th>
<th>No. neo HSV / Total</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>5/16 (33%)</td>
<td>OR 16.5 (4.1-65)</td>
<td>&lt;0.001</td>
<td>59.3 (6.7-525)</td>
</tr>
<tr>
<td>HSV-2</td>
<td>5/186 (2.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for new infection
Brown et al, JAMA 2003
# SEROPREVALENCE OF HSV IN AUSTRALIA

Cunningham et al, STI 2006

4000 randomly sampled sera (Ausdiab study)

<table>
<thead>
<tr>
<th>Section</th>
<th>HSV-2</th>
<th>HSV-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td>10.2%</td>
<td>67%</td>
</tr>
<tr>
<td>35-44</td>
<td>15.5%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>8.4%</td>
<td>71%</td>
</tr>
<tr>
<td>female</td>
<td>15.6%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Geography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>city</td>
<td>14.4%</td>
<td>74-79%</td>
</tr>
<tr>
<td>rural</td>
<td>8.7%</td>
<td>79%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.8%</td>
<td>75.7%</td>
</tr>
</tbody>
</table>
Compared anogenital specimens HSV-1 positive NSW Virol ref lab:

↑ HSV-13% 1980 to 41% in 2001.

Female sex and age under 25 were associated with a greater proportion of HSV-1 isolates in both time periods.

Haddow et al 2006
Treatment, Outcome
Neonatal HSV
Neonatal HSV - Investigations RX

- **Isolation/Detection of HSV from infant samples** e.g. skin lesion, nose, throat, conjunctiva swab
- **Skin lesion**: indirect IF (rapid)
- **CSF exam**
  - haemorrhagic encephalitis
  - HSV DNA PCR
  - Culture; better yield in newborn cf adults
- **CNS imaging; blood tests**
  - Blood: FBC, LFTs, coags,
- **Infant serology**: little role to play
# Neonatal HSV CSF examination Australia 1997-2011

<table>
<thead>
<tr>
<th>Investigation</th>
<th>White cell count</th>
<th>Red cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF cell count (No. /mm³), n=93</td>
<td>Mean Median Min, Max &gt;14/mm³</td>
<td>Mean Median Min, Max &gt;165/mm³</td>
</tr>
<tr>
<td>n=93</td>
<td>7595 0</td>
<td>19,741 82</td>
</tr>
<tr>
<td></td>
<td>n = 33 (38%)</td>
<td>n = 41 (35%)</td>
</tr>
<tr>
<td>CSF HSV DNA PCR, n=96</td>
<td>Positive</td>
<td>Positive with normal CSF WCC</td>
</tr>
<tr>
<td></td>
<td>36 (37.5%)</td>
<td>12</td>
</tr>
<tr>
<td>CSF HSV IgG, n=4</td>
<td>Positive</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>

*a Corrected for elevated red cell count where applicable*
**Recommended Antiviral Rx**

**Neonatal HSV Disease**

- Aciclovir 20mg/kg/dose given 8\textsuperscript{th} hourly

21 days if encephalitis/disseminated infection or LP not performed

14 days for disease localised to skin, eye or mouth

*Kimberlin et al, Pediatrics 2001*
Neonatal HSV infection
Management of recurrences

Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes
David W. Kimberlin, M.D., Richard J. Whitley, M.D., Wen Wan, Ph.D.,

- 74 infants: 45 CNS, 29 SEM
- Oral acyclovir 300mg/m²/dose tds for 6 mo post rx
- Better neurodevelopment after CNS disease
  * 60% vs 31% normal or mild impairment by Bayley
- Trend to neutropenia (0.09)
- NB - Small nos. esp HSV-1 CNS

Table 2. Demographic and Clinical Characteristics of Infants with and without 12-Month Bayley Scales of Infant Development Assessments.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CASG 103 (CNS) Study</th>
<th>CASG 104 (Skin, Eye, and Mouth) Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bayley Assessment (N=28)</td>
<td>No Bayley Assessment (N=17)</td>
</tr>
<tr>
<td>Gestational age — wk</td>
<td>39.5</td>
<td>38</td>
</tr>
<tr>
<td>Median</td>
<td>28-41</td>
<td>25-40</td>
</tr>
<tr>
<td>Range</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>HSV type — no./total no. (%)</td>
<td>I</td>
<td>7/19 (37)</td>
</tr>
<tr>
<td>II</td>
<td>12/19 (63)</td>
<td>11/11 (100)</td>
</tr>
<tr>
<td>White-cell count in cerebrospinal fluid at presentation — cells/mm³</td>
<td>65</td>
<td>71</td>
</tr>
<tr>
<td>Median</td>
<td>1-58,080</td>
<td>0-1216</td>
</tr>
<tr>
<td>Range</td>
<td>9/28 (32)</td>
<td>15/17 (88)</td>
</tr>
<tr>
<td>Evidence of HSV disease on MRI — no./total no. (%)</td>
<td>13/23 (57)</td>
<td>7/13 (54)</td>
</tr>
<tr>
<td>Abnormal EEG — no./total no. (%)</td>
<td>14/19 (74)</td>
<td>6/12 (50)</td>
</tr>
</tbody>
</table>
Prevention of Vertical transmission of HSV
Strategies to prevent neonatal HSV infection

- Pre/antenatal strategies to prevent maternal (genital) HSV infection
- Antenatal strategies to prevent transmission to the newborn
- Postnatal strategies to prevent infection of the newborns/ disease

http://www.spineguys.com/images/160w/52.gif
www.udel.edu/.../colorpage/cfr/cfras.GIF
www.thematrona.com/practice.html
Antiviral therapy during pregnancy

- Used in two ways
  - Rx severe/disseminated disease/
  - Prevent recurrence in third trimester in primary genital infection or frequent symptomatic past infection

- Balance potential risk to fetus with potential benefits of Rx
Multicenter case series
J Pediatr 2012: 161;134-138.e3

8 infants - neonatal HSV disease following maternal antiviral suppressive therapy during pregnancy
  - 6 mothers - first episode of genital HSV
  - 2 mothers prior Hx of genital HSV with no outbreak
  - Perinatal transmission in 7/8 infants
  - Intrauterine transmission 1/8

Suppressive therapy does not prevent neonatal HSV disease, which can have an atypical clinical presentation and drug resistance
Conclusions

* Although uncommon, neonatal HSV disease continues to cause significant mortality despite available therapies and sensitive diagnostic techniques in Australia.

* HSV-1 is the major serotype causing neonatal HSV disease in Australia.

* Still need rapid bedside test to guide empiric management of this rate, but devastating condition

* Further evidence of importance of active surveillance for rare diseases

* Paucity of evidence to guide Mx exposed asymptomatic infant and HSV in infancy beyond the neonatal period
To determine epidemiology, management outcomes of acute HSV infection in infants less than 12 months of age in Australia

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Acknowledgements

- Australian Paediatric Surveillance unit: contributors
- Members of APSU 1997-2011 HSV study team
  - D Isaacs, C Raynes-Greenow
- Sponsors of the APSU
  - NHMRC (Enabling Grant No. 402784);
  - Australian Government Department of Health and Ageing;
  - Sydney Medical School, University of Sydney