Troubled Waters
Hydrocephalus and the Preterm Infant
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Disclosure

• I have no actual or potential conflict of interest in relation to this program.

• I also assume responsibility for ensuring the scientific validity, objectivity, and completeness of the content of my presentation
Objectives

• Review Post Hemorrhagic Hydrocephalus as it relates to:
  – Preterm neurodevelopment/behavioral phenotype
  – Interventions & timing of interventions
  – Potentiation of initial injury
  – Future directions

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Introduction

“Who you are inside is what helps you make and do everything in life.” Fred Rogers
Introduction

- IVH devastating consequence of prematurity

- PHVD develops in ¼ as complication of IVH
  - Spontaneous arrest 2/3
  - Progression in 1/3*
  - Severe IVH (Grades III, PVHI) more likely

Case

- **Case 1**
  - 29 weeks gestation
  - Singleton
  - PVHI with PHVD
  - HUS with left fronto-parieto-occipital venous infarct

- **Case 2**
  - 26 weeks
  - Twin gestation
  - PVHI with PHVD
  - HUS with right fronto-parieto-occipital venous infarct
Case

- Case 1

- Case 2
PHVD-Management Options

• Diuretics $\rightarrow$ NOT recommended

• Fibrinolytic therapy $\rightarrow$ NOT recommended

• Serial tapping $\rightarrow$ NOT recommended*

• Ventriculoperitoneal shunts???
Outcome: Literature Review

Neurodevelopmental Outcome of Extremely Low Birth Weight Infants With Posthemorrhagic Hydrocephalus Requiring Shunt Insertion
Ira Adams-Chapman, Nellie I. Hansen, Barbara J. Stoll, Rose Higgins and for the NICHD Research Network
*Pediatrics* 2008;121:e1167-e1177; originally published online Apr 7, 2008; DOI: 10.1542/peds.2007-0423

### TABLE 4

<table>
<thead>
<tr>
<th>Outcomea</th>
<th>No IVH/No Shunt (N = 5163)</th>
<th>IVH 3/No Shunt (N = 459)</th>
<th>IVH 3/Shunt (N = 103)b</th>
<th>IVH 4/No Shunt (N = 311)</th>
<th>IVH 4/Shunt (N = 125)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI score</td>
<td>Mean (SE) 80.6 (0.25)</td>
<td>74.1 (0.91)</td>
<td>66.2 (1.72)d</td>
<td>71.5 (1.09)</td>
<td>60.3 (1.57)d</td>
</tr>
<tr>
<td>Median</td>
<td>82</td>
<td>75</td>
<td>61</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>MDI &lt; 70, n (%)</td>
<td>1318/4807 (27)</td>
<td>183/424 (43)</td>
<td>59/99 (60)a</td>
<td>143/295 (48)</td>
<td>87/115 (76)a</td>
</tr>
<tr>
<td>MDI = 49, n (%)</td>
<td>294/4805 (6)</td>
<td>70/424 (17)</td>
<td>32/99 (32)a</td>
<td>60/295 (20)</td>
<td>55/115 (48)a</td>
</tr>
<tr>
<td>PDI score</td>
<td>Mean (SE) 84.7 (0.25)</td>
<td>77.4 (0.97)</td>
<td>64.1 (1.88)d</td>
<td>73.2 (1.17)</td>
<td>55.2 (1.24)d</td>
</tr>
<tr>
<td>Median</td>
<td>87</td>
<td>82</td>
<td>51</td>
<td>75</td>
<td>49</td>
</tr>
<tr>
<td>PDI &lt; 70, n (%)</td>
<td>810/4741 (17)</td>
<td>140/417 (34)</td>
<td>65/100 (65)d</td>
<td>123/294 (42)</td>
<td>98/114 (86)d</td>
</tr>
<tr>
<td>PDI = 49, n (%)</td>
<td>313/4738 (7)</td>
<td>73/417 (18)</td>
<td>39/100 (39)d</td>
<td>76/294 (26)</td>
<td>74/114 (65)d</td>
</tr>
<tr>
<td>CP, n (%)</td>
<td>492/5125 (10)</td>
<td>103/457 (23)</td>
<td>58/102 (57)d</td>
<td>114/310 (37)</td>
<td>100/125 (80)d</td>
</tr>
<tr>
<td>Vision impairment, n (%)</td>
<td>465/5115 (9)</td>
<td>77/453 (17)</td>
<td>24/100 (24)</td>
<td>64/307 (21)</td>
<td>41/123 (33)e</td>
</tr>
<tr>
<td>Hearing impairment, n (%)</td>
<td>732/5037 (15)</td>
<td>578/453 (11)</td>
<td>21/101 (2)</td>
<td>127/294 (42)</td>
<td>81/114 (71)</td>
</tr>
<tr>
<td>NDI, n (%)</td>
<td>1690/4764 (35)</td>
<td>234/426 (55)</td>
<td>79/101 (78)d</td>
<td>189/299 (63)</td>
<td>114/124 (92)d</td>
</tr>
</tbody>
</table>

*a Information was missing for MDI (421), PDI (495), CP (42); vision impairment (63), hearing impairment (100), and NDI (447).

*b Statistically significant comparisons between IVH 3/shunt versus IVH 3/no shunt are shown. Comparisons between IVH 3/shunt versus no IVH/no shunt were statistically significant for all outcomes (P < .001) except hearing impairment (P = .56).

*c Statistically significant comparisons between IVH 4/shunt versus IVH 4/no shunt are shown. Comparisons between IVH 4/shunt versus no IVH/no shunt were statistically significant for all outcomes (P < .001 for all, except hearing impairment P < .01).

*d P = .001, e P = .01 for IVH 3/shunt versus IVH 3/no shunt or for IVH 4/shunt versus IVH 4/no shunt by the $\chi^2$ or Wilcoxon test.
Outcome: Literature Review

Outcome: Literature Review

Outcome: Literature Review

Outcome: Literature Review


- **Timing of intervention significant**

- **Developmental Quotient > 85:**
  - 94.6% of those not reaching 97%+4 mm
  - 70% of those treated after reaching 97%+4mm

- **VPS requirement**
  - 27% Early intervention
  - 72% Late intervention
# Outcome: Literature Review


<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>IQ</th>
<th>IQ &gt;85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>IVH III and IV</td>
<td>32</td>
<td>93 ± 16a</td>
<td>22 (71%)a</td>
</tr>
<tr>
<td>IVH III</td>
<td>17</td>
<td>96 ± 15</td>
<td>13 (76.5%)</td>
</tr>
<tr>
<td>IVH IV</td>
<td>15</td>
<td>91 ± 10a</td>
<td>9 (64.3%)a</td>
</tr>
<tr>
<td>IVH III &lt;p97+4 mm</td>
<td>11</td>
<td>99 ± 17</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>IVH III &gt;p97+4 mm</td>
<td>6</td>
<td>90 ± 10</td>
<td>4 (66.6%)</td>
</tr>
<tr>
<td>IVH IV &lt;p97+4 mm</td>
<td>6</td>
<td>95 ± 22a</td>
<td>3 (60%)a</td>
</tr>
<tr>
<td>IVH IV &gt;p97+4 mm</td>
<td>8</td>
<td>89 ± 15</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>IVH &lt;30 weeks</td>
<td>23</td>
<td>92 ± 17</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Controls</td>
<td>23</td>
<td>98 ± 15</td>
<td>17 (74%)</td>
</tr>
<tr>
<td>IVH III no VP shunt</td>
<td>9</td>
<td>101 ± 9</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>IVH III + VP shunt</td>
<td>8</td>
<td>90 ± 19</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>IVH IV no VP shunt</td>
<td>10</td>
<td>91 ± 19</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>IVH IV + VP shunt</td>
<td>4</td>
<td>90 ± 13</td>
<td>3 (75%)</td>
</tr>
</tbody>
</table>

*One child could not be tested.*
Outcome: Literature Review


- Early Intervention: less than 3 weeks of age
- 28 infants (13 early, 15 late)
- Less VPS dependence with early (61% vs. 93%)
- BSID II outcomes same (MDI 63)
- BSID III outcome:
  - Cognition 73 for early vs. 59 for late
  - Language 75 for early vs. 56 for late
Conundrum

• Outcomes more likely linked to:
  – Initial injury
  – Gestational age at time of injury
  – Timing of intervention

• Potential of PHH to exacerbate initial injury
Comparison of the preterm brain at 28 weeks’ gestational age (A) and the term brain (B) demonstrates increasing cortical development during the third trimester of gestation.

Ment L R Neoreviews 2000;1:e53-e57

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Pathogenesis
Interrupted Neuro-development

• Architectural changes to neuron

• Loss of subplate neurons, interneurons
• Arrest of OPC’s--->WM loss

• Neuronal loss
  – Thalamus
  – Basal ganglia
  – Cortical (parieto-occipital, sensorimotor, premotor, temporal, hippocampal)
  – External granule cells in cerebellum

• Gliosis
Pathogenesis
Interrupted neuro-development

- 3-4% with abnormality on HUS
- 20-65% with abnormality on MRI

“Tertiary” Brain Damage

Figure 2: Schematic representation of tertiary phase damage
Changes in oligodendrocytes, maturational blockade, and the production of glial scar products leading to decreased myelination, changes to glia, astrogliosis and microgliosis, and possible changes in EAA bioavailability are shown. Also shown is the NVU, a possible target for novel therapeutics because of its ability to mediate transmigration of inflammatory mediators. EAA= excitatory amino acid. NVU= neurovascular unit.

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Encephalopathy of the Preterm

• End result is:
  – Gray matter architecture distorted
  – White matter connectivity altered
  – Cerebellum under-developed

• PHH potentially:
  – Exacerbates initial injury
  – Exaggerates altered neural development

Behavioral Phenotype

• Describes a constellation of behavioral, cognitive, motor, and social difficulties observed in a population with a common biological disorder

• Premature survivors have a phenotype
  – Common biological disorder = brain injury
Behavioral Phenotype

• 50-70% in very preterm infants will have non-disabling (“minor”) morbidities

• Isolated ‘minor’ morbidity is rare
  – Cluster of conditions more common

Behavioral Phenotype

- Challenges to early identification
  - BSID not predictive of IQ
  - Discrete assessments needed
  - Sleeper effect

- Challenges may also contribute to difficulty assessing impact of PHH and intervention

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Behavioral Phenotype

- Preterm with:
  - Lower IQ than term
  - More likely to have borderline IQ

- Socially labile, anxious
  - Internalizing

- Preterms with greater:
  - Executive dysfunction
  - Hyperactivity, inattention
  - ADHD/ADD

Behavioral Phenotype

Preschool Performance of Children with Normal Intelligence Who Were Very Low-Birth-Weight Infants
Nancy Klein, Maureen Hack, John Gallagher and Avroy A. Fanaroff
Pediatrics 1985;75;531

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Case

Case 1
- Shunted at 6 weeks
- CP GMFCS I
  - Right hemiplegia
- Strabismus
- Development appropriate
- BSID III 100

Case 2
- Not shunted
- CP GMFCS IV
  - Left hemiplegia
- Optic nerve hypoplasia
- Seizures
- Developmental delay
- BSID III 70-80

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Conclusion

• Intervention thus far linked to major outcomes
  – Crude measures of ‘outcome’

• Functional outcomes essential

• No clear literature to guide management
Conclusions

• Cohorts
  – Canadian Neonatal Network
  – Neonatal Research Network
  – VT Oxford Network

• Research focus to shift
  – Early markers of dysfunction (EEG, biomarkers, MRI, neurologic exams)
Conclusion

• "Mom, on the way home tonight, can we go to the store to get a more comfortable crown for me?"
  Summer’s Blog (4.5y)
Thank You!

• Sunnybrook Health Sciences Centre
• Neonatal Follow Up Clinic
  – Marion DeLand, RN
  – Maureen Luther, PT
  – Denise Hohn, OT
  – Pat Maddalena, PNP
  – Laura Cooper, OT
  – Rudaina Banihani, MD (neo/developmental fellow) and Jessie VanDyk, MD (neonatal fellow)
  – Vanessa Warsh, administrator
  – Carol Grenade, administrator