RISK FACTORS FOR CEREBRAL PALSY IN PREMATURES

Nigel Paneth MD MPH
Michigan State University
AACPDM
September 11, 2014

This presentation is posted at http://www.epi.msu.edu/faculty/paneth
FIVE RISK FACTORS

(Not counting the severity of prematurity, with birth < 28 wks carrying a RR of about 50 compared to term birth)

1. Imaging evidence of brain damage
2. Prenatal infections
3. Features of mechanical ventilation
4. Low levels of thyroid hormone
5. Absence of Magnesium Sulfate in labor
1. BRAIN DAMAGE IMAGED ON ULTRASOUND

- Germinal matrix hemorrhage and intra-ventricular hemorrhage are not key determinant of outcomes.

- The key determinants of outcome are ventricular enlargement and parenchymal lesions on ultrasound, especially lucencies. These all carry relative risks of at least 10, compared to babies without such lesions.

- Absolute risk of CP in prematures with echolucent lesions approaches 50%.


2. THE FETAL INFLAMMATORY RESPONSE

Brain damage in many prematures is a result not of invasion of the brain by micro-organisms, but of a fetal inflammatory response to as yet unknown organisms, likely of uterine origin, that can both precipitate labor and cause white matter damage.

Obvious signs of perinatal inflammation (e.g. histologic chorioamnionitis, recovery of placental organisms) raise risk of CP modestly.

Recent evidence suggests that elevation of neonatal pro-inflammatory cytokines, especially if prolonged and of several classes of molecules also raises risk of CP.

Kuban KC et al J Child Neurol 2014 Mar 18. [Epub]
3. ODDS RATIOS FOR DISABLING CP BY VENTILATORY RISK FACTORS:

MV = mechanical ventilation; O = hyperoxia;
C = hypocarbia; P = prolonged ventilation for GA

### 4. LOW LEVELS OF THYROID HORMONE IN WEEK ONE OF LIFE AND RISK OF DCP

<table>
<thead>
<tr>
<th>Odds Ratio for DCP</th>
<th>Unadjusted</th>
<th>Adjusted for gestational age</th>
<th>Adjusted for GA and 15 other variables</th>
<th>Adjusted for GA and 21 other variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.6 (5.0-16.7)</td>
<td>10.8 (3.0-39.3)</td>
<td>3.5 (0.9-13.6)</td>
<td>4.4 (1.0-18.6)</td>
</tr>
</tbody>
</table>

5. MAGNESIUM SULFATE IN LABOR REDUCES RISK OF CP

- The unadjusted average rR of the four trials = 0.63
- 2012 Meta-analysis of observational studies = 0.64
- The multivariate RR in our 1998 cohort study = 0.63
STUDYING THE NEWBORN TRANSCRIPTOME IN CEREBRAL PALSY

Nigel Paneth MD MPH
Michigan State University
AACPD
September 11, 2014

This presentation is posted at http://www.epi.msu.edu/faculty/paneth
The “OMES” and their linkages

The DNA

The RNA transcripts of the epigenome.

The proteins coded for by the RNA transcripts.

The transcriptome, the proteome and the environment.

DNA that has been subject to DNA methylation and histone modification.
CP CASE-CONTROL STUDY

- 203 singleton CP cases age 2-16
- 203 matched controls:
  - birth year
  - gender
  - gestational age (< 28; 32-34; 35-37; >37 weeks)

- Exposure information:
  - maternal interview
  - birth certificates
  - maternal and infant birth hospital discharge abstracts

- Permission to obtain and study archived newborn blood spots from state of Michigan.
Michigan law mandates indefinite storage of this material and its consented use for scientific purposes.

Since 2009, spots have been frozen at -15 degrees C.
SOME EARLY FINDINGS ON THE FIRST 53 SINGLETON PAIRS

Z-STATISTICS OF RELATIVE MRNA EXPRESSION IN 53 CP CASE-CONTROL PAIRS: Seven pre-hypothesized gene sets reflecting four pathways. C, E AND G show statistically significant differences between cases and controls.
EXTRA SLIDES FOR DISCUSSION
Microarray Findings for Up, Down Regulation and Both for the Seven Hypothesized Pathways

53 singleton case-control pairs

<table>
<thead>
<tr>
<th>PATHWAYS</th>
<th>EFFECT SIZE*</th>
<th>DOWN</th>
<th>UP</th>
<th>BOTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canonical</td>
<td>-0.10</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Empirical</td>
<td>-0.19</td>
<td>&lt; .001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Thyroidal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canonical</td>
<td>-0.03</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Empirical</td>
<td>0.13</td>
<td>NS</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Asphyxial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canonical</td>
<td>0.18</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Empirical</td>
<td>-0.16</td>
<td>&lt;.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Coagulative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canonical</td>
<td>-0.08</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Gage t-statistic taken as a measure of effect size (Δ/σ)
Gene expression findings for three gene sets stratified by GA

<table>
<thead>
<tr>
<th></th>
<th><strong>Empirical inflammatory gene set</strong></th>
<th><strong>Empirical asphyxial gene set</strong></th>
<th><strong>Empirical thyroidal gene set</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean GAGE t-stat</td>
<td>P-values up</td>
<td>P-values down</td>
</tr>
<tr>
<td>≥37 weeks (n=33)</td>
<td>-0.42 NS</td>
<td>&lt;.001</td>
<td>-0.36 NS</td>
</tr>
<tr>
<td>&lt;37 weeks (n=20)</td>
<td>0.19 &lt;.01</td>
<td>NS</td>
<td>0.16 &lt;.05</td>
</tr>
</tbody>
</table>

Gage t-statistic taken as a measure of effect size (Δ/σ)