Studies of High Risk Infants: Implications for Cerebral Palsy and other Developmental Disabilities

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Learning Objectives

• Introduce High Risk Infant Follow-up Program and recent studies of High Risk Premature Infants
• Discuss implications for cerebral palsy and other developmental disabilities
• Discuss implications for early intervention service delivery

Biologic Risk

• Prematurity
• Hypoxemia/Ischemia
• Illness severity
• Brain injury
• Seizures
• IUGR
• Toxic substance exposure
**Biologic Risk – Etiology of Brain Injury**

- Advances in Neuroimaging - Multifactorial etiology
  - Hypoxia-ischemia (cv instability)
  - Excess release of glutamate
  - Genetic susceptibility
  - Growth factor deficiency
  - Oxidative stress
  - Maternal infections -> cytokines, inflammation
  - Toxins
  - Maternal stress or malnutrition

**Social and Environmental Risk**

- Significant relationship between poverty & poor developmental outcomes
- Pre and postnatal inadequate nutrition can lead to poor brain development
- Stressful events -> lasting adverse effects
  - mediated by:
    - genetic predispositions
    - supportive relationships

**Epigenetic Risk**

*Epigenetics: Experience Changes Genes*

Positive and negative experience leave chemical signals on genes that may be temporary or permanent and change how the gene supports learning.


**Epigenetics and Environmental Experience**

- Most studies in animal models
- Early life experiences in preemies alters the stress response and creates different stress response pathways from term babies.
- These altered response pathways disrupt normal brain growth and development.
- Animal studies suggest these changes can be passed to future generations
Science-Early Intervention
Beginning in the NICU

Recent Studies of NICU
Environmental Interventions

- Feldman (2014) RCT-14 daily skin to skin
  - 10 year better Executive Function measures
- Scher (2009) – RCT 8 weeks of skin to skin holding
  - better brain maturation by EEG
- Procainoy (2009) – RCT skin to skin and massage
  - Better developmental scores at age 2

Recent Studies of NICU
Environmental Interventions

- Guzetta (2011) – RCT massage 12 days
  - EEG worse in controls, intervention like term
- Milgrom (2010) – RCT parent training
  - DTI MRI - Better brain maturation
- Nordhov (2010) - RCT -7 sessions inpatient, 4 outpatient
  - Reading/supporting stress cues to promote self regulation and quiet alert state for social interaction
  - Better cognitive development at 3 and 5 years

Why Do We Need HRIF?

- Outcome studies
  - Risk
  - Odds
  - Percentages
High Risk Infant Follow-up

• **California Children’s Services**
  – Mandated Title 5 – Regional CCS approved NICUs must refer eligible babies to CCS approved HRIF program (3 visits to age 3yrs)
  – Unfunded – use their medical insurance
  – Some managed care systems not authorizing HRIF or authorize just the 1st visit

• Medical follow-up of neonatal issues
  • Growth
  • Neurological Exam
  • Developmental Assessment
  • Psychosocial Assessment
  • Guidance & connection to Early Intervention services

High Risk Infant Follow-up

Neurologic Exam
Movement & Posture

• Targeted to look for signs of cerebral palsy
• Amiel Tison exam
• GMFM levels

• Refer to CCS medical Therapy for PT & OT for:
  – children at risk for CP
  – < age 3 years
  – 2 Neurological physical exam findings

Cerebral Palsy

• Injury in the developing fetal or infant brain that results in abnormal development of movement and posture, and causes activity limitations

• Motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, behavior, and/or by a seizure disorder

Bax et al. 2005
Prevalence of Cerebral Palsy

<table>
<thead>
<tr>
<th>9 Europe Countries</th>
<th>88,371 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.9/1000 live births</td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>77/1,000</td>
</tr>
<tr>
<td>28-31 weeks</td>
<td>40/1,000</td>
</tr>
<tr>
<td>32-36 weeks</td>
<td>7/1,000</td>
</tr>
<tr>
<td>&gt; 36 weeks</td>
<td>1.1/1,000</td>
</tr>
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</table>

Himmelmann 2005

Cerebral Palsy

There is a range of severity

Diagnostic Imaging

- Preemies <1500 grams with grade I or II IVH
  - 3D MRIs near term age
- Cortical Gray Matter Volume was significantly reduced (Vasileiadis, PEDIATRICS 9/2004)
- Normal HUS/MRI adolescents born premature
  - Abnormal brain volumes & white matter abnormalities without distinctive injuries (Arthur, Pediatric Radiology, 2006)
- VLBW preemies at age 15 years >PWMI compared to Term and SGA controls (Vangerg, Neuroimaging, 11/2006, Norway)
- Grade I-II IVH – higher risk and rates of CP, DD, vision & hearing impairments (Lui, Pediatrics 2014;133:55–62)

White Matter Injury

Encephalopathy Of Prematurity (Volpe, 2009)

- PWMI and accompanying neuronal/axonal deficits -leads to deficit of mature oligodendrocytes, impaired myelination and decreased brain volume
  - Focal injury (<5%)
    - Deep in white matter
  - Diffuse
    - Noncystic and evolves over several weeks to form glial scars

- Focal or diffuse noncystic injury is emerging as the predominant lesion (Back, 2007, Stroke)

- Clinical MRI not able to detect diffuse micro-lesions that impair myelination – Dysmaturation (2014, Back, Clin Perinatology)
Normalizing MRI Reports

- Diffuse PWMI not seen readily on MRI
- Correlates reported as signal and diffusion abnormalities
  - increased T2 signal intensity in periventricular white matter can be injury or undermyelination associated with prematurity
  - NICU DC Summary reports Normal MRI
- What is Common in Preemies is Not Always Normal

T2 Weighted MRI Scans

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>47</td>
<td>85</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>%</td>
<td>28%</td>
<td>51%</td>
<td>17%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Total preemies < 32 weeks gestation $n = 167$

Woodward, NEJM 2006

Development of Immature Brains

Developmental skills are delayed at birth compared to term born peers

25 weeks GA - 39 Weeks GA

34 week brain is 60% of a term brain (Vohr, 2013)

Developmental Assessment

- Adjusted Age Scores
  (subtract # weeks early from age e.g. 8 month old born 16 weeks early = 4m AA)

- Chronologic Age Scores
  (score for age)

Are they catching up to chronologic same age peers?
### Developmental Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Specific Impairment</th>
<th>All</th>
<th>LBW 2500-1500 g</th>
<th>VLBW 1499-1000 g</th>
<th>ELBW &lt;1000 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory Vision Impairment</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4-24%</td>
<td>2-20%</td>
<td></td>
</tr>
<tr>
<td>Neurosensory Hearing Loss</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>1-3%</td>
<td>7-11%</td>
<td></td>
</tr>
<tr>
<td>Developmental Cerebral Palsy</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>6-20%</td>
<td>9-30%</td>
<td></td>
</tr>
<tr>
<td>Speech Language Delay</td>
<td>6%</td>
<td>3-5%</td>
<td>8-45%</td>
<td>25-45%</td>
<td></td>
</tr>
<tr>
<td>Learning/ Academic Learning Disabilities</td>
<td>5-20%</td>
<td>17%</td>
<td>30-38%</td>
<td>34-45%</td>
<td></td>
</tr>
<tr>
<td>Special Education</td>
<td>8%</td>
<td>8%</td>
<td>60-70%</td>
<td>24-80%</td>
<td></td>
</tr>
<tr>
<td>Behavioral ADHD</td>
<td>5-7%</td>
<td>7-30%</td>
<td>9-30%</td>
<td>5-40%</td>
<td></td>
</tr>
</tbody>
</table>

Vanderbilt 2007

### Preemie Graduate Services

#### Long Term Morbidities

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Preemie Graduate Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>Memory deficits</td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>Mental Health Disorders</td>
</tr>
<tr>
<td></td>
<td>ADHD, Autism, Schizophrenia</td>
</tr>
<tr>
<td>Speech-Language deficits</td>
<td>Learning differences</td>
</tr>
<tr>
<td>Coordination/balance</td>
<td>Executive Function- Attention, organization difficulties</td>
</tr>
<tr>
<td>Visual-motor perception</td>
<td>Processing problems</td>
</tr>
<tr>
<td>Social/ emotional</td>
<td></td>
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### Preemie Project: Medical-Legal-Community Collaborative

#### Preemie Project

- Longitudinal study of preterm children as part of a community-based collaborative that promoted early access to intervention services.
- All children born <37 weeks gestational age (GA) and <2500 grams and met one California Children Services risk factor for developmental delay.
### Developmental Catch-Up

**Average Range 85-115**

<table>
<thead>
<tr>
<th>Percent Of Preemies With Standard Scores ≥ 85</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
</tr>
<tr>
<td>~2yr</td>
</tr>
<tr>
<td>~3yr</td>
</tr>
</tbody>
</table>

**DeBattista, 2008**

### Individual Trajectories 4m-36m

![Individual Trajectories 4m-36m](image)

### When do Preemies Catch-up to Term Peers in Development?

- Historically – Gessell
  - Automatic Sequential Catch up
- Web MD 2009
- AAP 2013
- Parent Blogs
Development in Adaptive Behavior to Age 3

ML Logistic Regression for P(VABC>85)

Linear and Quadratic Time

Probability of Other Score > 85

DeBattista, 2013

Trajectory Categories

Developmental Trajectory Vineland Adaptive Behavior Composite

Developmental Categories (%)

- Catch-up (8)
- Sustained Normal (49)
- No Catch-up (16)
- False Catch-up (27)

Vineland Trends by Domain

Adaptive Behavior by GA Group
Preemie Catch Up

- Extensive systematic review of medical and psychological literature

- Promoting that preemies “catch up by age 2 years” is not evidence based practice
Guidance & Early Intervention (EI)

- California Early Start Program
  - Federal Extension of IDEA legislation for children birth to 3 years
    - Therapies and Infant Programs for children with Developmental Delays & Disabilities

Early Start Program

- California budget cuts 2009
  - NICU grads no longer eligible at discharge based on risk
  - Families must use private insurance up - before Early Start will provide service

Eligibility Categories:

- Developmental Delay
  - Percent delay
    - < 2 years adjusted age score: 33% delay in 1 domain
      - 22m/18m function < 12m in one area
    - > 2 years chron age: 50% delay in 1, or 33% in 2 domains
      - 22m/18m function < 9m in one area

- Established Risk

- Solely Low Incidence

National EI Trends

- Nationally, only 17% of children who are younger than 5 years and whose development was classified as delayed actually received services for those delays (Rosenberg, 2008)
  
- NICHD Neonatal Network (Hintz, 2008) <1000 gm preemies born 1997-2000 (n= 2,315) up to 44% had not received any EI services by the 18-22month visit.
Preemie Project EI Dosage

- Hours of early intervention data collected (ESP nurse, teacher, PT, OT, SLP) targeting development
- Entered into Mixed Multilevel Model
  # hours for each child between clinic assessment visits (time varying covariate)
- EI was associated with lower adaptive behavior scores at baseline (more delayed got EI)
- **Every hour of EI service** resulted in a positive increase in scores over time

Summary

- Children born prematurely:
  - have immature brains subject to injuries
  - lower group mean scores- persist into adulthood
  - greater numbers requiring special education
  - limited access to EI
  - are expected to automatically catch up
  - NICU Early interventions are not considered in Federal Part C service provision and are not consistently provided

Summary

- Developmental outcomes are impacted by biologic, social and epigenetic risk
- We can’t predict exact outcomes for individual babies
- There is nothing magical about age 2 for preemie catch-up

Summary

- Research knowledge -> **increased**:
  - understanding of neuropathology & genes
  - understanding of the importance of environmental experiences on brain development beginning in the NICU and continuing through childhood

- **Decreased** investment in resources to promote development with early and sustained environmental experiences and therapies
Summary

- We need a renewed investment in Early Intervention for High Risk Infants!
- Development is shaped by a dynamic and continuous interaction between biology and experience

(National Council on the Science of Early Intervention 2001)

Thank you