Encephalopathy of Prematurity

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Long Term Outcome for Very Preterm Infants

- 4%-5% risk of cerebral palsy, with 50% having an increased clumsiness and reduced physical ability
- 25%-50% of children requiring educational assistance in school
- 25% developing behavioral problems including ADHD, social maladjustment at school and anxiety
How can we define brain injury in the premature infant?

VLBW

Perinatal Practices
Steroids, BP, Nutrition

ALTED BRAIN DEVELOPMENT

Social and environmental factors

OUTCOME

BRAIN INJURY
What are the causes for adverse neurodevelopmental outcomes?

• Brain Injury
  • Intraventricular hemorrhage
  • White matter injury
  • Cerebellar hemorrhage

• Brain Development
  • Defining the nature of altered brain development
  • Factors driving alterations in brain development
    • The environment and exposures
Intraventricular Hemorrhage (IVH)
Grades of IVH
Grade IV intracranial hemorrhage is typically associated with spastic hemiparesis.
Intraventricular Hemorrhage in the Preterm Infant

Prospective registry of 34,646 infants 22-28 weeks EGA at 26 Neonatal Research Network centers from 1993-2012

- Survival increased for infants ≥ 23 weeks (varied by age)
- Reduction in intracranial hemorrhage for infants 26-28 weeks EGA, but not 22-25 weeks
  - Antenatal steroids increased 24% → 87%
  - Intubation decreased 80% → 65%

Periventricular Leukomalacia (PVL)
White Matter Abnormalities

Terminology
- White matter cysts
- White matter punctate lesions
- Loss of white matter volume
- Diffuse high signal changes throughout white matter

Predictors for MRI White Matter Injury

• SEPSIS

• Maternal factors
  • Fever ($p=0.01$)
  • Sepsis at delivery ($p=0.03$)
  • Chorioamnionitis

• Infant factors
  • Ischemia
    • IVH ($p=0.015$)
    • PDA ($p=0.001$)
    • Inotropes ($p=0.002$)
  • Sepsis/NEC during hospital course ($p=0.03$)

White Matter Abnormalities

Is brain injury the major factor driving adverse neurodevelopmental outcome?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
<th>No.</th>
<th>MDI Score (SD)</th>
<th>MDI&lt;70 No. (%)</th>
<th>PDI Score (SD)</th>
<th>PDI&lt;70 No. (%)</th>
<th>Cerebral palsy No. (%)</th>
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<td>86.4(17.9)</td>
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Axonal injury

- Pre-OL dysmaturation
- Axonal (afferent/efferent) degeneration

- Myelination
- Cortical and thalamic development

Pre-OL injury

- Pre-OL dysmaturation
- Axonal (afferent/efferent) degeneration

- Myelination
- Cortical and thalamic development
Neuron Deficit in the White Matter and Subplate in Periventricular Leukomalacia

Hannah C. Kinney, MD,¹ Robin L. Haynes, PhD,¹ Gang Xu, MD, PhD,¹
Sarah E. Andiman, AB,¹ Rebecca D. Folkerth, MD,² Lynn A. Sleeper, ScD,³
and Joseph J. Volpe, MD⁴

40% reduction in neuronal density in subplate with PVL

Late Development of the GABAergic System in the Human Cerebral Cortex and White Matter

Gang Xu, MD, PhD, Kevin G. Broadbelt, PhD, Robin L. Haynes, PhD, Rebecca D. Folkert, MD, Natalia S. Borenstein, MS, Richard A. Belliveau, BA, Felicia L. Trachtenberg, PhD, Joseph J. Volpe, MD, and Hannah C. Kinney, MD

Migrating GABAergic neurons increase in cerebral white matter from 20 to 40 wks and peak at term. 70 – 80% reduction with PVL
A Pre-OL injury

- Pre-OL dysmaturation
- Axonal (afferent/efferent) degeneration

  - Myelination
  - Cortical and thalamic development

B Axonal Injury

- Pre-OL dysmaturation
- Axonal (afferent/efferent) degeneration

  - Myelination
  - Cortical and thalamic development

C Thalamic Injury

- Axonal (afferent/efferent) degeneration
  - Pre-OL dysmaturation
  - Myelination
  - Cortical development
  - Thalamic development

D SPN Injury

- Axonal (afferent/efferent) degeneration
  - Pre-OL dysmaturation
  - Myelination
  - Cortical and thalamic development

E Migrating GABAergic neuron injury

  - GABAergic neurons
  - Cortical development (upper cortical layers)
Summary of Brain Injury

• Traditional Forms of Brain Injury
  • IVH, PVL, CBH

• Widespread (invisible) Brain Injury
  • Axons, thalamus, subplate, migrating GABAergic

• Down- and Up-Stream effects of Brain Injury
  • Deafferentation resulting in neuronal death
  • Alterations in cell fates/development
  • Impaired signaling at critical stages in development
Can we define the nature of alterations in brain development – the role of advanced imaging?
Cortical Folding in the NICU

25 weeks

30 weeks

Term (38 weeks)

Rapid and extensive folding during 3rd trimester
Cortical folding

25 week

30 week

33 week

Term equivalent (37 weeks)

Adult

Term control

Image courtesy of Terrie E. Inder, MBChB, MD.
Surface reconstructions from Images obtained at term equivalent
Comparison of Sulcal Depth Maps

39 weeks 7 years

Alterations in Brain Development in VPT infants

VPT-born (n=24) vs term-born (n=24) subjects at 7 years

Sulcal depth

Volumetric ROI’s

\[ t\text{-statistic} \]

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-4 \\
-1.5 / 1.5 \\
4 \\
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ARE traditional medical factors mediating the alterations in brain development?
## Pain and Neonatal Stress

<table>
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<tr>
<th>Average daily Neonatal Infant Stressor Scale score</th>
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<tbody>
<tr>
<td>First 14 days (mean ± SD)</td>
<td>106 ± 13</td>
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<tr>
<td>First 28 days (mean ± SD)</td>
<td>102 ± 18</td>
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<tr>
<td>Admission until term equivalent/discharge (mean ± SD)</td>
<td>80 ± 12</td>
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<table>
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<th>Average daily number of procedures</th>
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<tbody>
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<td>First 14 days (mean ± SD)</td>
<td>11 ± 4</td>
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<tr>
<td>First 28 days (mean ± SD)</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>Admission until term equivalent/discharge (mean ± SD)</td>
<td>7 ± 3</td>
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</table>

Increased stress associated with decreased frontal lobe width, abnormal temporal lobe diffusion and neural networks (after adjusting for confounders of immaturity, length of ventilation, CRIB score, sepsis +).

Mean functional connectivity correlation maps generated using the right temporal lobe seed in (A) term control infants (n=10) (B) low-stress infants (n=10), and (C) high-stress infants (n=10). Illustrated quantity is Fisher z-transformed correlation coefficient.

Neonatal pain and developmental outcomes in children born preterm: a systematic review.

In infants born extremely preterm (gestational age ≤29 wk) greater numbers of painful procedures were associated with

• delayed postnatal growth
• poor early neurodevelopment
• high cortical activation
• altered brain development
• poor quality of cognitive and motor development at 1 year of age
• changes in cortical rhythmicity and cortical thickness in children at 7 years of age.
So if the infants are suffering from pain, then should we provide analgesia?
Neonatal morphine exposure in very preterm infants—cerebral development and outcomes.

- Participants (n = 223) were assessed. Fifty-seven participants received morphine in the NICU (median cumulative dose \(0.7 \text{ mg/kg}\), IQR 0.1-0.95 mg/kg, range 0.1-5.3 mg/kg). Thirty-two participants received only boluses; 21 received a mixture of boluses and infusion; 4 received an infusion only; no clinical factors differed between these 3 subgroups.

- At term, preterm infants who received morphine had a trend toward smaller cortical volumes in the orbitofrontal (\(P_{\text{left}} = .002, P_{\text{right}} = .01\)) and subgenual (\(P_{\text{left}} = .01\)) regions. At 7 years, cortical volumes did not differ.

- At 7 years no impact of morphine on neurobehavioral outcome were observed.
Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine

Jill G. Zwicker, PhD, OT(C)1,2,3, Steven P. Miller, MDCM2,3,4, Ruth E. Grunau, PhD2,3,5, Vann Chau, MD4, Rollin Brant, PhD3,6, Colin Studholme, PhD7, Mengyuan Liu, BS7, Anne Synnes, MDCM2,3,5, Kenneth J. Poskitt, MDCM3,8, Mikaela L. Stiver, BSc4, and Emily W. Y. Tam. MDCM4

![Graph showing cerebellar volume vs. cumulative morphine (mg/kg)]

Brain injury and development in preterm infants exposed to fentanyl.

- Seventy-eight infants (76%) received fentanyl (median cumulative dose 3 µg/kg, interquartile range 1-441 µg/kg). Cumulative fentanyl dose in the first week of life correlated with the incidence of cerebellar hemorrhage after correction for covariates (odds ratio 2.1, 95% CI: 1.1-4.1).

- Cumulative fentanyl dose before term equivalent age correlated with reductions in transverse cerebellar diameter after correction for covariates, including the presence of cerebellar hemorrhage (r = 0.461, P = 0.002).
Use of Opiates and Benzodiazepines

NOT DRUGS

- Facilitated tuck (arms/legs in flexed position)
- Music Therapy
- Skin-to-skin contact ("kangaroo care")
- Infant massage
- Breastfeeding
- Nonnutritive sucking
- Developmentally appropriate care
  - Limited environmental stimuli
  - Lateral positioning
  - Supportive bedding
  - Attention to behavioral cues
Nonnutritive Sucking or Facilitated Tuck

Joan Smith – The M-Technique

Image courtesy of Terrie E. Inder, MD.
Pilot Study in Preterm Infants >30 Weeks

Each infant received standard neonatal intensive unit (NICU) care or standard NICU care plus a 7-minute M-Technique session, 6 times per week for 5 weeks.

An increased growth velocity (P = 0.005).

**Infant Massage**

**Neurodevelopment at 2 years corrected age.**

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<th>Control group $(n = 38)$</th>
<th>Intervention group $(n = 35)$</th>
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<td>82.9 ± 5.61</td>
<td>85.1 ± 1.99</td>
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<td>84.2 ± 6.28</td>
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<td>70–84</td>
<td>13 (36.1)</td>
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<td>$&lt;70$</td>
<td>3 (7.9)</td>
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<td>70–84</td>
<td>8 (21.1)</td>
<td>6 (17.2)</td>
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Sleep deprivation, pain and prematurity: a review study.

- Importance of sleep in preterm infant with the need to spend 75% of time in sleep
- Development of circadian rhythm from 18 weeks
- Frequent disturbance of infant
- Lack of recognition of caregivers for sleep state
- Importance of kangaroo care or skin to skin for promoting sleep
- Inter-relationship of pain and poor sleep
The Neonatal Intensive Care Unit Environment

• Noisy, chaotic

• Exceeds sound and light recommendations from the AAP
  • Understood to adversely affect growth and development

• Sound abatement in the NICU is important
  • Developmental care
  • Family centered care

• Entered a period of rapid change in NICU design
  • Renovations to private rooms
The Developmental Effects of the NICU
Single Patient Room

Image courtesy of Terrie E. Inder, MD.
Study NICU

• ½ single patient rooms
  • 168 square feet
  • 3 walls; 4th wall is a sliding glass door
  • Individualized lighting
  • Parents can visit 24 hours a day
    • Lounger at the bedside for parents to sleep on

• ½ open bay beds
  • Approx 10-12 beds in 1100 square feet of space
  • General lighting
  • Screens can be pulled to bedside for privacy
  • Parents can visit 24 hours a day
    • Sleep rooms available just outside the NICU

Images courtesy of Terrie E. Inder, MD.
Follow up at age 2 years

• 86 infants (83%) returned for developmental follow-up
  • Mean (SD): 27.4 (2.1) months

• Associations between room type and cognitive, language and motor outcome were explored, while controlling for:
  • CRIB score
  • Cerebral injury
  • Social risk score
  • Family functioning
*p=0.006
$\beta = -8$
(-14, -2)

*Linear regression; controlling CRIB, cerebral injury, social risk and family functioning
Hemispheric Asymmetries

Single Patient Room

Open Bay

More than just auditory experience

The Journal of Pediatrics • www.jpeds.com

A Risk of Sensory Deprivation in the Neonatal Intensive Care Unit

Alan H. Jobe, MD, PhD
Harry Harlow Rhesus Monkey Work

Photo by Al Fenn | The LIFE Picture Collection
Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life.


• 73 premature infants and 73 matched controls

• 1 hour of Kangaroo Care each day for 14 days

• Improved autonomic control at term and improved

• Improved cognitive development throughout the first 10 years associated with better parent-infant interaction
Can we measure distress – skin conductance?

Photo by Dmitry Kalinovsky | shutterstock
Skin Conductance Amplitude During Pain

Does skin-to-skin contact reduce stress during diaper change in preterm infants?

Fig. 1 Skin conductance peaks per sec before, during and after diaper change. In both groups there was a significant increase from before to during diaper change (p < 0.05). There was a significant difference between the groups only at time point durin...

Advantages of Single Family Rooms

Improved Outcomes

• SFR NICU was associated with a 2.55-point increase in Bayley cognitive scores and 3.70-point increase in language scores.
  • Prior work appears to be strongly mediated by the presence of parents

• Every 10 mL/kg/day increase of human milk at 4 weeks was independently associated with increases in Bayley cognitive, language, and motor scores (0.29, 0.34, and 0.24, respectively).
Extreme Prematurity

Brain Injury

NICU experiences

Parenting Family environment

Social influences

Alters normal brain development

Constitutional factors

Neurobehavioral Outcome
Extreme Prematurity

Brain Injury

Traditional – IVH, PVL, CBH
Invisible – Thalamus, subplate, interneurons

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Increase ANS, delayed cord clamping
Minimize handling, BP therapy, opiates
Reduce CLABSI, sepsis, NEC

Neurobehavioral Outcome
Extreme Prematurity

NICU experiences
- Parenting
  - Family environment
- Social influences

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- Constitutional factors
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- Invisible – Thalamus, subplate, interneurons
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Alters normal brain development

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NICU experiences

Negative: Pain, isolation
Positive: Nurturing

Parenting
Family environment

Social influences

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Neurobehavioral Outcome
Department of Pediatric Newborn Medicine

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Alters normal brain development

Neurobehavioral Outcome

Increase ANS, delayed cord clamping
Minimize handling, BP therapy, opiates
Reduce CLABSI, sepsis, NEC

Traditional – IVH, PVL, CBH
Invisible – Thalamus, subplate, interneurons

Negative: Pain, isolation
Positive: Nurturing
Caring in the NICU

Our past
The Boston Lying In Hospital

Our present
Brigham NICU care

Our future
As bright as the stars
The New, Improved World of Infant Care

A host of high-tech advances are giving newborns a better shot at avoiding a range of ailments. The long-term impact could be profound.

Six research centers are trying to identify the causes of premature birth, which can cause serious and costly disabilities. PHOTO: JUSTIN METZ FOR THE WALL STREET JOURNAL
Summary

• Brain Injury is important to reduce
• Many forms of brain injury in the preterm infant remain invisible
• Injury has a prolonged secondary dysmaturation effect – protracted vulnerability
• Experience and exposures alter brain development during this CRITICAL period of brain development to term equivalency
• Reduce adverse experience – pain, negative handling, alarm noise; as pain, stress and sensory isolation appear to adversely influence brain structure and outcome
• Increase positive experience – mother’s voice; music; skin-to-skin and touch therapy.
• Parental mental health, empowerment and attachment are also powerful for outcomes
• Take care of the caregivers – wellbeing of the providers