The Importance of Long-term Follow-up of High-Risk Newborn Infants: Lessons from NICHD-funded Research Studies

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Greetings from the NIH
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Disclosure

➢ I have no financial or commercial conflicts of interests to declare.

➢ I will not present information on any non-approved products or services

Outline & Learning Objectives

1. Why follow-up?
2. Lessons from perinatal interventions
3. Preterm infant outcome statistics
4. Neuro-rehabilitation and infant brain plasticity

Why Follow-up?

President John F. Kennedy, signing HR 1109 on October 17, 1962, creating NICHD

“…Research in recent years has established beyond question that adult behavior, intelligence, and motivation are established by the experience and patterns of response developed in the formative years of life…”

Why Follow-up?

A world to be born under your footsteps
Mrs. John F. Kennedy

Why Follow-up?
Additional Reasons for Follow-Up Research

- Effects of diseases on growing and maturing organs
  - Maturations vary in pace and trajectories
- Long-term consequences of diseases
  - Chronic lung diseases increasing the risk for pneumonia
- Effect of interventions
  - Have the benefits persisted?
  - Unintended consequences
- Factors affecting outcomes help understand disease mechanisms and processes of resiliency
- Treatment interventions: Research and individual care

Growth & Maturation Interruption

- Brain
- Lungs
- Heart
- GI tract and digestive organs
- The Kidneys
- Other systems:
  - Autonomous systems
  - Sleep
  - The Immune System
  - Metabolic systems

Preterm birth --- interrupted growth and maturation!

19 weeks

Full term infant

5 year old child.

Huang et al, NeuroImaging, 35: 2006

Ventricles, caudate nucleus & basal ganglion

19 weeks

Full term infant

5 year old child.

Huang et al, NeuroImaging, 35: 2006
**Hippocampus, thalamus & ganglionic eminence**

Huang et al., NeuroImaging, 33: 2006

**Development of the Human Cerebral Cortex**

Hanks courtesy Dr. Tessaak Kinney, 2003

Golgi drawings: Chen and Armstrong, 2002

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**The Kidneys**

Nephron Numbers

- Nephrion numbers:
  - Term ~ 750,000
  - 32 weeks: <500,000
  - 27 weeks: <300,000


**Oligonephropathy of Preterm Birth & Adult Diseases**


**The Lungs**

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FIGURE 2
Late gestation is critical for nephrogenesis
Hinchliffe & Cebrid

Lessons from Long-term Follow-Up Research on Practice

- Apgar Score and Association with CP
- Antenatal steroid
  - How consensus conference changed practice
  - How “repeated courses” of steroid therapy was stopped
- MgSO4 to reduce CP in VLBW infants
- Hypothermia for neonatal encephalopathy
- Other therapies
  - Caffeine for Apnea, surprising benefit on CP rate
  - iNO for preventing BPD: no effect

How did Apgar Scores & CP got Associated?

- Dr. Virginia Apgar developed her “score” in a cafeteria on a napkin, while explaining to a student how to examine a newborn infant at birth
- The “score” was a means of communication—not for predicting outcomes, NOT for CP prediction!
- Over time, “low Apgar score” (anything less than 10) became synonymous with a risk for CP
- An NIH-funded long-term study—demystified the Apgar score—CP connection myth

National Collaborative Perinatal Project

- Enrolled ~54,000 women from 12 perinatal centers across the US (in the 1959s to 66s)
- Apgar scores given by independent specially-trained observers not responsible for clinical care 1 and 5 minutes in all; up to 20 minutes if needed
- Children followed at 1 and 7 years of age
- Results:
  - Most patients with CP had Apgar Scores 7 or more
  - About 20% of all CP cases could be attributed to adverse perinatal events

* Nelson KB & Ellenberg H. Pediatrics 1981; 68:36-44
Apgar Scores as Predictors of Chronic Neurologic Disability

- >75% of CP infants had > 7 Apgar Scores at 5 minutes

Nelson, KB, Ellenberg, JH. PEDIATRICS Vol. 68 No. 1 July 1981

Antenatal Steroid Story

- In 1972 Liggins and Howie studied antenatal steroid effects on infants: (n=213 women): (Pediatrics 1972)
  - RDS: 9% in treated ; 26% in control
  - Death: 3% in treated; 15% in control
- In 1994: Only ~ 20% of eligible women were receiving antenatal steroids
- In 1994 NIH Consensus Development Conference
- Practice changed: In the NICHD Neonatal Research Network hospitals ANS use was:
  - 1990-91: 20%
  - 1995-96: 71%
  - 1997-2000: 79%

If a little bit is good…. ....a lot may be better!

- Trials in the late 1990s showed that repeat courses of antenatal corticosteroids improved minor respiratory outcome variables (duration of oxygen therapy, slightly less severe RDS)
- But such treatment also reduced birth weights and increased IUGR rates.
- Yet, repeated course of ANS was being practiced widely through much of the 1990s

Long-Term Outcomes after Repeat Doses of Antenatal Corticosteroids

Wapner RJ et al. NEJM; 357: 2007

- NICHD-MFMU Network study:
  - Repeated course of steroid: 248 infants
  - A single course of steroid: 238 infants
  - Physical exam and Bayley test at ~ 30 months CA
- Bayley scores and growth parameters were similar
- Cerebral Palsy: Six children in the repeat-corticosteroid and one child in the single course of steroid group
  - (RR, 5.7; 95% CI, 0.7 to 46.7; P = 0.12).
- No real benefits with repeated courses
- Possibility of harm: so use repeated courses?

Neuro-Protection Strategies

1. Magnesium sulfate to reduce CP in very-low birth weight infants
2. Mild therapeutic hypothermia for neonatal encephalopathy
42 VLBW infants with CP born in 4 California counties between 1983-1985 were compared with 75 non-CP
Focus: antenatal exposure to MgSO4 (tolocolysis, prevent seizure in preeclampsia/eclampsia)
Maternal MgSO4 was 36% in the controls (48/75) with no-CP, but only 7.1% (17/42) infants with CP. (OR 0.14, 95% CI, 0.05, 0.51).
The study “suggested” a protective effect of maternal exposure to MgSO4 to prevent CP in VLBW infants
Prospective studies were then launched to test the effect of MgSO4 in preventing CP in VLBW infants

Summary of MgSO4 & Cerebral Palsy: Systematic Review
Conde-Agudelo, A, Romero R. AJOG June, 2009

2658 fetuses exposed MgSO4: ~30% fewer CPs (95% CI: 12% to 45%)

Nelson, KB, Grether, JK. PEDIATRICS Vol. 95; February 1995
Summary of MgSO4 & Cerebral Palsy: Systematic Review
Conde-Agudelo, A, Romero R. AJOG June, 2009

But, wait for the surprise!

Conclusions: Magnesium sulfate given to pregnant women at imminent risk of birth before 30 weeks’ gestation did not improve neurological, cognitive, behavioral, growth, or functional outcomes in their children at school age; a mortality advantage cannot be excluded. The lack of long-term benefit requires confirmation in additional studies.

School-age Outcomes of Very Preterm Infants After Antenatal Treatment With Magnesium Sulfate vs Placebo

RESULTS There were 1255 fetuses known to be alive at randomization. Of 867 survivors available for follow-up, outcomes at school age (corrected age 6-11 years) were determined for 669 (77%). There was little difference between groups on any of the cognitive, behavioral, growth, or functional outcomes.

Hypothermia for Neonatal Encephalopathy

Shankaran et al, NEJM 2005

Questions?
- Do the beneficial effects remain into childhood?
- Did hypothermia reduced mortality at the expense of increasing rates of neurological disabilities in the survivors?

“Use the latest medicine immediately upon its discovery, before its effectiveness vanishes…”

Sir William Osler


Hypothermia for Neonatal Encephalopathy

Shankaran et al, NEJM 2005

- Cooling to 33.5 degree for 72 hours (n=208)
  - Mortality: 37% control, 24% cooled
  - Moderate to severe CP: 30% control, 19% cooled
  - Death or moderate to severe CP: 62% control 44% cooled

Questions?
- Do the beneficial effects remain into childhood?
- Did hypothermia reduced mortality at the expense of increasing rates of neurological disabilities in the survivors?
**Preterm infant outcome Survival Rates**

- A cohort of 4446 infants born in NRN hospitals @ 22-25 weeks of GA
- 83% received intensive care
- Outcomes known for 94% @ 18-24 months
- GA, BW, sex, antenatal steroids used to develop a calculator

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**Extremely Low Gestation Infant Outcomes: 2008**

- Preterm: 11-12% of ~3.8 million births ~500,000
- Late Preterm: 9% or ~360,000
- Moderate Preterm: 2% 29-33 weeks: ~80,000
- ELGAN: ≤28 weeks ~1% or ~40,000
- In the late 1970s, early 1980s:
  - <28 weeks: 90% mortality and >50% of survivors had serious neurological disabilities
- In the 2010s:
  - <28 weeks survival rate ~80%
  - Disability rates ~20-30%
A Major Evolving Topic: Adults Born Preterm

**Cardiovascular:** Larsson SC, et al. Int J Cardiol. 2014 Oct 23
**Metabolic Syndrome:** Kajantie E, et al. J Clin Endocrinol Metab. 2014 Oct
**Hematological:** Zöller B, et al. Pediatrics, 2014
**CNS Outcomes:** Kalpakidou AK, et al. 2014
**General Health:** Roberts et al. Semin Fetal Neonatal Med. 2014

Lessons Learned from Follow-Up Research Studies

- Improved obstetric care is the reason for continued improvement in neonatal outcomes
- “Three letter” conditions make things worse: ICH, PVL, ROP, NEC, BPD
- Human milk/breastfeeding improves neurological outcome
- Good parenting/ maternal, paternal IQ/SES improves outcome
- Higher “lost-to-follow-up” rates worsens reported rates of poor outcomes
- CNS status might improve, or worsen over time

Lost-to Follow-up Rates & Neurodevelopmental Impairments

- 42 publications on follow-up examined:
- 34,185 infants: follow-up rates ranged 71% to 100%
- The higher the lost-to-follow-up the higher the rates of reported NDI
- Good follow-up is good practice!

Outcome rates can change over time

- In 1983, data of a unique nationwide cohort of 1338 very preterm (<32 weeks of gestation) or VLBW (<1500 g) infants in the Netherlands was collected and followed at several ages until they reached the age of 19 years.

New Frontier: Power of Parenting

<table>
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<th>Age (years)</th>
<th>Handicap assessed (N)</th>
<th>Major handicap (%)</th>
<th>Minor handicap (%)</th>
<th>Disability (%)</th>
<th>Normal (%)</th>
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<td>944</td>
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<td>12%</td>
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<tr>
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<tr>
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<td>6%</td>
<td>16%</td>
<td>28%</td>
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<tr>
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<td>765</td>
<td>4%</td>
<td>8%</td>
<td>40%</td>
<td>47%</td>
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</tbody>
</table>

* Percentages after multiple imputation analysis [5].
Maternal Education and Neurodevelopmental Outcome: Composite IQ Trajectories


- Increasing IQ of the infant over the years with higher maternal educational levels

The Power of Parenting...

How Might it Work?

- Quality and quantity of cognitive stimulation
  - Reading, talking and play time with your child
- The parenting style: friendly, reassuring and firm
- Better parental health behavior; sibling effects
- Affordability for better school choices
- Access higher quality follow-up care facilities
- Breastfeeding; better nutrition

Good Parenting & Neuro-Rehabilitation

Importance of sensory function to brain development

Courtesy: Nathalie Maitre, MD, Vanderbilt University


Importance of sensory function to motor development

Courtesy: Nathalie Maitre, MD, Vanderbilt University

Gait-activated Functional Electrical Stimulation (GAFES)

Basis of Neuro-rehabilitation

- CP is a non-progressive disorder but functions of affected children can be improved, with far-reaching implications.
- The sensory system can be harnessed to rewire the bodies and brains of children with CP.
- More research is underway in this field.

Evidence of Plasticity

- 27 weeks gestation
- Had massive IVH
- Porencephalic cyst
- Hemiplegic CP.
- His fMRI at age 7

Evidence of Plasticity

- IQ at age 4 exceeded the scale: 185
- At 11 he is in 7th grade, and 3 months away from black belt in Tae Kwon Do
- Rock climbing without adaptive equipment
- Fluent in French and taking Astronomy 102 at Vanderbilt University
- His long-term goals are to become the Director of NASA, so he can “be the boss of space discovery”.
- So much for IVH!!

Some Famous High-Risk Infants

- Prematurity
  - Moses ? (born after 6 months and 1 day)
  - Richard III
  - Jonathan Swift
  - Isaac Newton
  - Victor Hugo
  - Voltaire
  - Thomas Hardy
  - Anna Pavlova
  - Sydney Poitier (born 1927)

- Asphyxia at Birth
  - Samuel Johnson
  - Goethe
  - Christopher Wren
  - Franklin Roosevelt
  - Picasso
Dr. Robert Aldrich (1918-1998)
The First Director of the NICHD

How Dr. Robert Aldrich Became the First Director of NICHD
- In 1962, the NIH director Dr. James Shannon offered the position to Dr. Aldrich
- Dr. Aldrich declined
- A few days later, telephone rang, and it was President Kennedy, who offered the job to Dr. Aldrich
- Dr. Aldrich again declined the offer

- A few minutes later the telephone rang—this time it was the President of the University
- Unhappy that Aldrich had declined an offer by the President of the United States, harming the reputation of the University
- “You are fired,” shouted the University President

How Dr. Robert Aldrich Became the First Director of NICHD
- As Dr. Aldrich was recovering from his shock and disbelief, the telephone rang again
- The voice on the other end said: “Hi, this is President Kennedy calling again. I understand you are out of a job. I have something in mind you might be interested in…”
- Dr. Aldrich moved to Bethesda in 1963 as the first Director of NICHD
- The rest, as they say, is history.
The little ones leaped, and shouted, and laughed. . . And all the hills echoed. . .

William Blake

Thank you...