Iron Deficiency and the Developing Brain

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Learning Objectives

Define the common causes of iron deficiency in newborn infants and toddlers

Identify the regions of the brain that are particularly vulnerable to early childhood iron deficiency

Characterize the behaviors that are affected by early life iron deficiency
Overview

Why worry about iron?
Nutrient-brain interactions - why the brain needs iron
Iron needs in infancy
  - Sequelae of iron deficiency
Fetal and neonatal iron
  - Term and preterm infants
  - Sequelae of iron deficiency

Why Worry About Iron Deficiency?

2 billion people world-wide are iron deficient (WHO)
  - 30-50% of pregnant women
Every cell/organ system needs iron for proper development and subsequent function
Iron deficiency anemia is associated with clinical symptoms
  - Due to tissue level ID
  - Symptoms occur prior to anemia
Main reason to worry is the effect on the developing brain
  - Cognitive and motor effects
  - Some temporary (while ID), others long-term (after iron repletion)
  - The long-term effects are the real cost to society
    • Increased depression, anxiety, risk of schizophrenia, autism
    • Loss of job and educational potential

Early Nutrition and Brain Development: General Principles

Positive or negative nutrient effects on brain development

Based on...
Timing, Dose and Duration of Exposure
Kretchmer, Beard, Carlson, 1995
**Nutrient-Brain-Behavior Relationships**

Various brain regions/processes have different developmental trajectories

The vulnerability of a brain region to a nutrient is based on
- When nutrient deficit/overload is likely to occur
- Brain's requirement for that nutrient at that time

Behavioral changes must map onto those brain structures altered by the nutrient effect

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**Iron: A Critical Nutrient for the Developing Brain**

Iron containing enzymes and hemo-proteins are involved in important cellular processes in developing brain
- Delta 9-desaturase, glial cytochromes control oligodendrocyte production of myelin
- Cytochromes mediate oxidative phosphorylation and determine neuronal and glial energy status
- Tyrosine Hydroxylase involved in monoamine neurotransmitter and receptor synthesis (dopamine, serotonin, norepi)
- ID affects genome while ID and long after ID is treated
Iron Deficiency in the Infant or Toddler (6-24 months)

Factors Determining Infant Iron Status

The Differential Effect of Timing of ID on Brain Development

Iron at Birth

Iron Needs

Available Iron

Iron Losses

Infant Iron Status
ID in Infancy: Who is at risk?

Most postnatal ID is due to inadequate dietary intake ± low stores at birth ± blood loss

- Low stores at birth
- Inadequate dietary intake
  - Low iron formula
  - Breast milk
  - Early change to cow milk
- Blood loss
  - Hemorrhage at birth (anemia)
  - Parasitic infection, food intolerance (GI loss)

Brain Development Affected by ID in Infancy

Human Brain Development

Neurobehavioral Sequelae of Early Postnatal Iron Deficiency in Humans

Over 50 studies demonstrate dietary ID between 6 and 24 months leads to:

- Behavioral abnormalities (Lozoff et al, 2000)
  - Motor and cognitive delays while iron deficient
  - Cognitive delays 19-23 years after iron repletion
    - Arithmetic, writing, school progress, anxiety/depression, social problems and inattention (Lozoff et al, 2000)
  - Characteristic of monoamine and hippocampal dysfunction
- Electrophysiologic abnormalities (delayed ABR latencies)
  - At 6 months while iron deficient (Roncagliolo et al, 1998)
  - At 2-4 years after iron repletion (Algat et al, 2003)
  - Characteristic of impaired myelination
Effect of Iron Deficiency in Infancy on General Cognitive Performance

(B Lozoff et al)

Effect of Iron Deficiency in Infancy on Affect and Engagement

Courtesy of B. Lozoff

Effect of Iron Deficiency in Infancy on Affect and Engagement

Courtesy of B. Lozoff
Motor Coordination and Affect in Human Toddlers: a Dose Response Effect (Lozoff et al, 2008)

What is the Biology? Major Dopamine Pathways Connecting to Prefrontal Cortex

Neurotransmitter Effects in the Rat

Effects on monoamines, esp dopamine, known since late 1970’s (studies by Yehuda, Youdim, Beard)

While ID: Decreased DAT, D1R, D2R and increased SERT
  – Regional differences- Large effects in striatum, ventral midbrain
  – Changes related to timing and severity (E Unger et al, 2012)
Slower Nerve Conduction Velocity:
Evoked Potential Latencies 3 Years after Iron Rx

What is the Biology?
Myelin Effects in the Rat

- Altered fatty acid profile in myelin fraction
- Decreased myelin proteins, including myelin basic protein
- Decreased oligodendrocyte proliferation

Transcripts for myelin basic protein affected
- Short term (while ID)
- Long term (at P180 after iron repletion)

(Studies by Connor, Clardy, Rao)

Brain Development Affected by Fetal/Neonatal ID

Human Brain Development

- Presynaptic terminal development
- Synapse formation
- Synaptic pruning
- Regional brain growth
- Myelination
- Cognitive development
- Late infancy/Adolescence
Fetal Iron: Endowment and Distribution

Fetuses have 75mg of elemental iron per kilogram body weight during 3rd trimester
- Term infant: 250mg
- 24 weeker (500g): 37.5 mg

Majority is in the RBCs (55mg/kg)
Liver storage pools are relatively large at term (12 mg/kg); serum ferritin >40 mcg/L
Non-storage tissues, including brain, heart, skeletal muscle account for the rest (8 mg/kg)

What Can Negatively Affect Neonatal Iron Status?

Decreased maternal iron supply
- Fetus with very iron deficient mother (Hgb<8.5)
- Common (>30%) in developing countries
- No studies of newborn brain iron status

Decreased placental iron transfer during gestation
- Prematurity
  - Iron accreted during third trimester
  - Generally negative iron balance during NICU stay
- IUGR due to maternal hypertension during pregnancy
  - 50% affected
  - 75,000 infants per year in US
  - 32% decrease in brain iron concentration (Georgieff et al, 1995)
- Early cord clamping

Term Infants:
What Can Negatively Affect Neonatal Iron Status?

Diabetes Mellitus during pregnancy
- Chronically hypoxic fetus (IDM) => Increased erythropoiesis
- 65% affected
- 150,000 infants per year in US
- 40% decrease in brain iron concentration (Petry et al, 1992)

Basic principle:
Iron prioritized to RBCs over brain & other organs when Fe demand> Fe supply
Factors that Determine Preterm Infant Iron Status in the NICU

Negative Iron Balance
- Low Endowment (IUGR)
- Phlebotomy Losses
- Iron Rx at 2 months
- Iron Rx < 2mg/kg/d
- RhEpo Rx
- Rapid Postnatal Growth

Positive Iron Balance
- Older gestation & AGA
- RBC Transfusion
- Iron Rx at 2 weeks
- Iron Rx @ 2-4 mg/kg/d
- Iron Rx @ 6mg/kg/d c rhEpo
- Parenteral Iron
- Slow Postnatal Growth Rate

Preterm infants have elevated ZnPP at 34 weeks PCA (Winzerling & Kling, 2001)

Neurobehavioral Sequelae of Fetal and Neonatal ID
Fewer studies than in postnatal ID
- Decreased maternal iron status
  - increased risk of schizophrenia in offspring (Issel et al, 2008)
  - increased risk of autism in offspring (Schmidt et al, 2014)
- Term infants with low neonatal iron stores have
  - impaired auditory recognition memory processing (Siddappa et al, 2004)
  - poorer school age neurodevelopment (Tamura et al, 2002)
  - worse immediate and delayed recall at 3.5 y (Friggs et al, 2003)
- Preterm infants with iron stores at 36 weeks PCA
  - more abnormal reflexes (Armany-Sivan, 2006)
  - longer conduction times on BAER (Armany et al, 2010)
- Early iron supplementation in preterms => higher mental processing composite score at 5.3 years (Steinmacher et al, 2007)

SUGGESTS SIGNIFICANT HIPPOCAMPAL AND MYELIN IMPAIRMENTS

What is the Biology?
Hippocampal Effects: Rodent Models
Short and long-term genomic changes (ES Carlson et al, 2007)
- Dendritic structure, synaptic efficacy, oxidative metabolism
Reduced energy status (M deUngria et al, 2000)
Glutamate and GABA sequestration (R Rao et al, 2003)
Altered dendritic morphology (ES Carlson et al, 2009)
Long-term suppression of BDNF and its receptor (P Tran et al, 2009)
Reduced LTP (long-term potentiation) (Piasensky et al, 2013)
Reduced learning and memory
- Morris Water Maze (B Felt and B Lozoff, 1996)
- Radial Arm Maze (AT Schmitt et al, 2007)
Summary

- Iron plays a critical role in early neurodevelopment
- Early iron deficiency without anemia affects brain function
- ID brain/behavior alterations persist after resolution of ID
- Early detection of at-risk infants is crucial for brain health
- Need new tools to detect pre-anemic iron deficiency

References


Conceptual Model of Neurodevelopmental Effects of Early Iron Deficiency