Iron Deficiency and Neurological Consequences for Children

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NORTH AMERICA



EUROPE

AFRICA



Objectives:

- Understand the epidemiology, etiology, and consequences of iron deficiency
- Understand brain iron metabolism and the impact of its deficiency on the developing brain
- Identify neurological conditions which are associated with iron deficiency to ensure prompt diagnosis and treatment

Global Epidemiology of Anemia

- 24.8% of population (1.62 billion)
  - Highest in pre-school aged children 47.4% (CI: 45.7-49.1)
  - School-aged children 25.4% (CI: 19.9-30.9)
  - Pregnant women 41.8% (CI: 39.0–43.8)
- Canadian Estimates:
  - Pre-school aged children 7.6% (CI:1.6–28.9%)
  - Pregnant women 11.5% (CI:2.4-40.9%)

de Benoist B et al., eds. **Worldwide prevalence of anaemia 1993-2005.** WHO Global Database on Anaemia Geneva, World Health Organization, 2008.
http://www.who.int/vmnis/anaemia/prevalence/summary/anaemia_data_status_t2/en/

How Common is Iron Deficiency?

- More common in developing countries
- Also occurs in industrialized nations
  - Edmonton study of 32, 069 12 to 59 month old children May 2002-June 2008
    - 7.69% of 19 month-old children had IDA; 11.65% ID

    Paediatrics and Child Health. 2009 May/June;Vol 14 Suppl 14A:44A
  - Canadian high risk populations - excess of 50%
- Most vulnerable - poorest, youngest, least educated, female - at highest risk

What Causes of Iron Deficiency?

- Life-stages
  - Menarche
  - Infancy/early childhood
- Nutritional deficiency
- Cultural practices
- Parasites
  - Hookworm
- H. Pylori



How is Iron Utilized?

- Iron exists as two pools:
  - Stored iron (2/3)
  - Functional iron(1/3)
    - Hemoglobin 70%
    - Transport iron 25%
    - Myoglobin 4%
    - Enzyme related 1%
- Biochemical effects of ID
  - DECREASED:
    - Heme proteins
    - Iron containing enzymes
    - Iron as cofactor



Why is Iron Important?

- Vital micronutrient
  - Hormones
  - Neurotransmitters
  - RNA and DNA metabolism
  - Myelin production
  - energy metabolism
- Production of hemoglobin



IRON DEFICIENCY: Spectrum of Hematological Changes

Mild Iron Deficiency	**Decrease Iron Stores**	**Increased RDW**
Moderate Iron Deficiency	**Decrease Iron Transport**	**Decreased Serum Iron, Changes in Transport Proteins**
Severe Iron Deficiency	**Iron Deficient Erythropoiesis**	**Hypochromic Microcytic Anemia**

Ensuring Adequate Iron Intake is Important

- Iron maintains normal cellular function
- Deficiency effects every organ system
- Most obvious clinical effect is anemia
- Critical to diagnose and treat early in children

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IRON IN THE DEVELOPING BRAIN



Brain Iron

- Iron enters brain via receptor mediated endocytosis
- 50% of brain iron is acquired during the first 3 weeks of life
- Transport within brain poorly understood
  - Most associated with transferrin, ferritin, lactoferrin, enzymes
  - “Free” iron has been implicated in the pathophysiology of a number of brain diseases
- Distribution is uneven
- Present in grey and white matter
- Most commonly found in oligodendrocytes
  - Normal oligodendrocytes, brain iron, and iron transport are required for myelin production and maintenance

Iron Deficiency and the Developing Brain

- Decreased brain iron and ferritin
  - Compensatory increase in transferrin
  - Non-homogeneous decrease in brain iron
- Abnormal Myelination
  - Iron is a cofactor for lipid and cholesterol biosynthesis
  - Rats with prenatal and lactational iron deficiency have a delayed rate of myelination and hypomyelination
- Neurochemical Abnormalities
  - GABA, dopamine, serotonin, phenylalanine
- Abnormal Neurodevelopment
  - Rat and murine models - irreversible changes in motor and cognitive development
  - Rat model - association between iron deficiency and SNHL
  - Hippocampus – disrupted plasticity

Neurological Consequences of Iron Deficiency in Children

DEVELOPMENTAL DELAY

DEVELOPMENTAL ABNORMALITIES

- ID negative impact on cognition, behavior and motor skills
- ID, IDA and non-ID anemia can cause cognitive defects at any age
  - Hemoglobin level correlates to cognitive performance
  - Impact of iron therapy to improve cognitive function is unclear
- Lozoff and colleagues followed a cohort of Costa Rican children from infancy to adolescence to determine the early effects of iron deficiency on childhood development

FIRST STUDY: Infants and toddlers

- 191 well infants 12 to 23 months
- Baseline, 1 & 12 wk post therapy lab work and BSID
- Infants with moderate to severe IDA had lower baseline MDI and PDI scores
- 1 week - no change in MDI or PDI scores
- 12 weeks - moderate to severe IDA
    - lack of correction of iron stores with correction of anemia (25/34 patients) correlated with persistence of lower MDI and PDI scores
- Iron therapy to correct anemia alone is not adequate to correct neurodevelopmental disturbances

Conclusion: Early, severe, chronic iron deficiency is more likely to result in neurodevelopmental abnormalities

Pediatrics 1987;79:981-995

SECOND STUDY: School-Age Children

- Follow-up study at 5 years of age to determine effects of iron deficiency in infancy on later development
- Retention rate: 85%
- All had normal growth and nutritional status
- moderately severe anemia in infancy resulted in significantly lower scores on mental and motor testing

CONCLUSION: Children with iron deficiency anemia in infancy are at risk for long-lasting developmental sequelae

NEJM 1991;325:687-694

THIRD STUDY: Adolescents

- Longitudinal follow-up to determine effects of iron deficiency in infancy on later intellectual functioning
- Retention rate: 87%
- Adolescence with moderately severe iron deficiency in infancy:
  - had lower test scores in numerous areas
  - more likely to have repeated a grade/ received tutoring
  - more behavior problems

CONCLUSION: Severe chronic iron deficiency in infancy identifies children at risk for abnormalities in behavior, cognition and motor skills more than ten years after iron therapy

Pediatrics 2000;105(4):1-11

HOW DOES IRON DEFICIENCY RESULT IN DEVELOPMENTAL DELAY?

- Alterations in hippocampus
- Mitochondrial damage
- Abnormal myelination
- Neurotransmitter abnormalities
  - Brain dopamine metabolism
- Behavioral abnormalities due to iron deficiency impair learning capability

Neurological Consequences of Iron Deficiency in Children

CEREBROVASCULAR EVENTS

How Common are Cerebrovascular Events in Children?

- Incidence: 2 - 3/100 000 children per year
- No etiology found
    - 20 - 36% ischemic stroke
    - 16% hemorrhagic stroke
- Many case reports and larger studies demonstrate an association between iron deficiency and pediatric stroke in otherwise well children

IRON DEFICIENCY: A CAUSE OF STROKE IN CHILDREN

- Retrospective review of children from the neonatal period to age 15 years who presented with stroke between 1985 and 1995.
- 53 patients diagnosed
  - 2.5/100 000 children per year
- 16/53 (30.2%) no etiology found
  - 6/16 (37.5%) with etiology undetermined were iron deficient ($p<0.01$)
- Of these children:
  - All were 6 - 18 months
  - All had a mild viral illness
  - Not all were anemic
  - Not all had thrombocytosis

CONCLUSION:

- An association between iron deficiency and pediatric stroke exists in children 6 to 18 months of age in the setting of a nonspecific viral illness

Hartfield et al. Pediatric Neurology 1997;16(1)50-53

Further work in this area:

- *Azab et al. Ann Hematol 2014;93(4):57:1-6*
  - Case-control study of 21 patients with 100 controls
  - Healthy children with stroke were 3.8 times more likely to have IDA (p=0.005)
  - Recommend early detection of IDA for prevention of health problems
- *Maguire et al. Pediatrics 2007;120:1053-1057*
  - Case-control study of 53 patients 12-38 months
  - otherwise health children were 10 times more likely to be iron deficient
  - accounted for more than 50% of stroke in the cohort
  - Concluded that iron deficiency is a risk factor for stroke in children
- *Sebire et al. Brain 2005;128:477-489*
  - Study of 42 patients with SVT from 4 stroke registries
  - 55% had anemia; 50% had ID
  - More common in otherwise health children (p=0.07)
  - Concluded - nutritional deficiency modifiable risk factor

Mechanism of ID and Stroke

- Thrombocytosis secondary to iron deficiency
- Iron deficiency leads to a hypercoagulable state
- Anemic Hypoxia
- Abnormalities in mitochondrial function

Neurological Consequences of Iron Deficiency in Children

FEBRILE SEIZURE

Febrile Seizures

- 2-5% of children up to 5 years of age
  - Peak age is 18 months - similar to ID
- Known risk factors:
  - Genetics, fever >39.4 celsius, particular infections, day-care attendance, low birth weight, neonatal stay > 30 days, maternal smoking in pregnancy

Role of Iron Deficiency in Febrile Seizures

- Susceptibility of developing brain to seizures related to maturational changes in excitatory and inhibitory neurotransmitters
- Inappropriate response to cytokines associated with infection

Relevant Studies:

- One study found ID to decrease the risk of febrile seizures in children
  - Kobrinsky NL, Yager JY, Cheang MS, et al. J Child Neurol. 1995 (2):105-109

- Six studies found ID to increase the risk
  - Sharif M, et al. Global J of Health Sci 2016 8(2):185-189
  - Papageorgiou V, et al. Eur J Paediatr Neurol 2015 19(5):591-6
  - Hartfield et al. Clinical Pediatrics February 2009 48(4):420-426
  - Rehman N, Billoo SG. JCPSP, 2005 (5): 338-340
  - Daoud AS, Batieha A, Abu-Ekteish F, et al. Epilepsia, 2002 (7): 740-74
  - Pisacane A, Sansone R, Impagliazzo N, et al. BMJ,1996 (313):343-344

- Difficulties with these studies:
  - Some are small studies
  - Diagnostic criteria used to diagnose ID/IDA
    - Iron studies inaccurate in the setting of febrile illness

Consensus:

- Iron deficiency is a risk factor for febrile seizure
- Children with febrile seizures should be screened for ID/IDA
  - Avoid iron studies while acutely unwell

Neurological Consequences of Iron Deficiency in Children

BREATH HOLDING SPELLS

Breath Holding Spells

- Occur in 27% of children
- Proposed to be due to autonomic dysregulation and vagally mediated cardiac arrest with cerebral anoxia
- Iron Deficiency exacerbates BHS as:
  - Anemia decreases oxygen carrying capacity causing cerebral anoxia
  - ID children are more irritable which increases likelihood of a BHS
  - Iron is a cofactor in the enzymes that degrade cerebral catecholamines
    - Autonomic dysregulation
  - Abnormality in neurotransmitter function

Iron Therapy and Breath Holding Spells

- Considered randomised/quasi-randomised studies
- Compared iron supplementation with placebo or no therapy for children < 18 years with BHS
- Reduction in frequency or severity or both
- RESULTS:
  - 2 studies with 87 children
  - Iron decreased frequency (OR 76.48 95% CI: 15.65-373.76, P<0.00001)
  - Meta-analysis solely examined iron causing complete resolution maintain significance (OR 53.45: 95% CI 6.57-434.57, P=0.0002)
- CONCLUSION:
  - Iron therapy is effective in the treatment of BHS

Cochrane review: Zehetner A et al. Cochrane Database Syst Rev 2010 12 (5)

Is Iron Therapy Appropriate for BHS for Children Without Anemia?

- Prospective study of 100 children 6-26 months with BHS
- 73% resolution and 23% had 50% reduction in BHS
  - 3 mg/kg/day of iron for 12 weeks
- Factors predicting poor response on univariate analysis:
  - Frequency of attacks and intolerance of iron
- Response rate not predicted by presence of anemia or iron status

Conclude: Iron therapy is effective therapy in BHS regardless of iron status

Jain R et al. J of Paediatr Child Health 2017 June 1 ePub

How to Approach Children with BHS?

- Investigate for IDA
- Treat those with IDA and ID
- For those without ID/IDA
  - More research needed!
  - Discuss risks/benefits of therapy
  - Trial 3 mg/kg/day
  - Monitor side-effects

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Other Less Common Problems

Iron and Dysphagia

- Plummer-Vinson Syndrome is well described in adults
  - Rare reports in children - youngest 5 years
  - Treatment is iron
  - Dysphagia resolves prior to webs/rings
- Adults complain of oral pain when ID
- Esophageal manometry (adults)
  - Abnormal in ID adults with dysphagia without webs/rings
- Animal models of ID
  - Abnormal esophageal muscle structure in ID
  - Nitric Oxide
    - required for normal smooth muscle function/peristalsis
    - decreased as production is iron dependent

ID AND DYSPHAGIA: IMPLICATIONS FOR INFANTS

- Toddlers develop IDA as consume excessive milk
  - Typically refuse solids
  - Mostly thought of as a "parenting" issue
- *New hypothesis:* Mild ID results in oral pain and dysphagia. This causes feeding dysfunction, which perpetuates the ID state. Rapidly reversible with iron therapy
- Supported by adult and animal studies
- Warrants further study

Hartfield. Clinical Pediatrics, February 2010

Recognized and Rare

- *Pseudotumor cerebri*
  - Iron deficiency recognized cause of pseudotumor cerebri since the 1800's
  - Pathophysiology uncertain
    - Tissue hypoxia leads to cerebral edema
    - Abnormal hemodynamics result in increased CBF resulting in increased ICP
    - Depletion in iron-containing enzymes may have effect
  - Reversible with iron therapy
- *Cranial nerve palsy*

New and Emerging

- *ADHD*
  - Abnormalities in dopaminergic function
  - Meta analysis- low serum ferritin and not iron associated with ADHD

  Wang Y et al. PLoS One 2017 12(1)
- *Restless Leg Syndrome*
  - Publications implicate ID as a contributor to RLS
  - Meta-analysis of iron therapy – insufficient evidence to determine benefit

  Trotti LM et al. Cochrane Database Sys Rev 2012 May 16(5)

Conclusions

- Iron is required for:
  - Brain development
  - Myelination
  - Neurotransmitter production
  - Hemoglobin synthesis
- Deficiency associated with a variety of neurological problems

Prevention of iron deficiency throughout gestation, infancy and childhood is imperative for normal neurodevelopment and to prevent other important complications of iron deficiency

Strategies to Prevent Iron Deficiency

- Screen and treat pregnant women for ID
  - More prevalent in women of child bearing age
- Delayed cord clamping
- Ensure appropriate diet at early check-ups
  - Iron containing food introduced by 6 months
  - Avoid cow's milk until 1 year of age
  - Breastfeed or formula with iron before then
- Screen high risk infants and children
  - Indigenous, immigrants, premature infants
- Remember - parasites and H. Pylori contribute
- Timely therapy with diagnosis