SICKLE CELL DISEASE & IRON OVERLOAD

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ANPA 2012

DISCLOSURES

- Formerly Speakers Bureau:
  - Novartis for Exjade®; Deferasirox 2006-2007

GOALS & OBJECTIVES

- Brief review of Iron homeostasis & overload
- Sickle cell hemoglobinopathy and the heightened complication of transfusional hemosiderosis
- Advances in Management: Diagnosis & therapy with emphasis on cardiac complications.

ANNOUNCEMENT:

Professor Theodosia McMoli
June 15th 1938 to June 5th 2012

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iron homeostasis & transfusional iron overload (hemosiderosis)
Body Iron Distribution and Storage

- Dietary iron
- Plasma transferrin
- Storage iron
- Iron loss
- Fatty acid
- Adenosine
- Vitamin A
- glucocorticoids
- Estrogens
- Thyroid hormones
- Prolactin
- Renal tubular cell

Basic Causes of Iron Overload
- Acquired iron overload
  - Transfusional
  - Ineffective erythropoiesis
  - Toxic ingestion (very rare)
- Hereditary
  - HFE hemochromatosis
    - Homozygous C282Y mutation in HFE gene
  - Defective regulatory receptor in intestine results in increased absorption of iron
  - Other genetic mutations
- Iron overload can result in iron-related dysfunction of key organs

Iron Loading From Blood Transfusions
- 1 unit of blood contains approximately 200 mg of iron
  - Chronic transfusion-dependent patients have an iron excess of ~0.4 to 0.5 mg/kg/day
- There is no physiologic mechanism to remove excess iron
- Therefore, iron accumulates with repeated blood transfusions
- Signs of iron overload can be seen anywhere between 10 and 20 transfusions

Iron Overload
- Iron overload
- Serum transferrin iron binding capacity exceeded
- NTBI circulates in the plasma
- Excess iron promotes free radical formation
- Insoluble iron complexes are deposited in body tissues
- Cardiac
- Liver
- Pancreas
- Reproductive
- Endocrine

Transfusional Excess Iron Can Build Up in Key Organs

Diseases With High Risk of Iron Overload

- Diseases requiring frequent or repeated transfusions
  - β-Thalassemia (major and intermedia)
  - Sickle cell anemia
  - Myelodysplastic syndromes (MDS)
  - Aplastic anemia
  - Rare chronic anemias
    - Blackfan-Diamond anemia (red cell aplasia)
    - Fanconi anemia (hypoplastic anemia)
    - Others

Sickle Cell Disease

- Sickle cell disease (SCD) is an inherited disorder characterized by chronic hemolytic anemia, organ dysfunction and pain
- In African Americans, SCD occurs in 3 of every 1,000 live births
  - Estimates indicate that SCD affects more than 75,000 African Americans
  - Nigeria: About 100,000 LIVE BIRTHS per year

Some Genotypes of SCD

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Abbreviated Form</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Homozygous SCD</td>
</tr>
<tr>
<td>B</td>
<td>Sickle cell-hemoglobin C disease</td>
</tr>
<tr>
<td>C</td>
<td>Sickle cell-thalassemia (specify β⁺/β⁻)</td>
</tr>
<tr>
<td>D</td>
<td>Sickle cell-other Hb variant (e.g., E)</td>
</tr>
</tbody>
</table>

Risk of Stroke in SCD

- ~11% of patients with SCD have stroke by age 20
- ~22% had previous stroke or "silent" transient ischemic events
- Patients with previous stroke have increased risk of second stroke
  - Chronic transfusions can decrease incidence of second stroke

Transfusion Therapy in SCD

- Reasons for transfusion
  - Stroke prevention
  - Acute or chronic lung disease (acute chest syndrome, chronic hypoxia, or pulmonary hypertension)
  - Intractable pain
  - Priapism
  - True symptomatic anemia (not due to sickle symptoms)
- Types of transfusions
  - Intermittent simple transfusion "as needed"
  - Chronic simple transfusion
  - Exchange transfusion

Stroke Prevention Trial in Sickle Cell Anemia: STOP Trial Design

After 2 TCDs ≥200 cm/sec, children age 3–16 years with SCD were randomized

Standard care (incl. occasional transfusion) (N = 67)

Transfusion to HbS <30% (N = 63)

Endpoint: Incidence of stroke (cerebral infarction or intracranial hemorrhage)
STOP Trial Results

NHLBI Recommendation for SCD Stroke Management

STOP 2 Trial Design

Discontinued Transfusion Program (N = 41)
Continued Transfusion Program (N = 38)

Optimizing Primary Stroke Prevention in Children With Sickle Cell Anemia: STOP 2 Trial Design

Endpoint: stroke or reversion to abnormal TCD

Summary of STOP and STOP 2 Trials

STOP 1
- Transfusion therapy reduced risk of first clinical stroke >90% (P < 0.001) versus standard care in children with abnormal TCD

STOP 2
- Continuing transfusion therapy reduced risk of stroke and reversion to high-risk status by ~50% (P < 0.001)

STOP Trial Results

Number of Patients

STOP Study halted prematurely in 1997

NHLBI = National Institutes of Health; SCD = sickle cell disease; STOP = Stroke Prevention Trial in Sickle Cell Anemia; TCD = Transcranial Doppler


NHLBI Recommendations for SCD Stroke Management

- TCD screening for all children with SCD
- Transfusion therapy for children with abnormal TCD
- Continuing transfusions indefinitely in high-risk children
- Management of iron overload for children on chronic transfusions

Summary

- Transfusions are critical in treating or reducing certain disease complications such as acute chest syndrome and stroke
- Many patients with SCD are chronically or intermittently transfused
- STOP trial results confirm benefits of transfusion therapy in stroke reduction
- Chronically or intermittently transfused patients with SCD are at high risk for iron overload

NHLBI = National Heart, Lung, and Blood Institute; SCD = sickle cell disease; TCD = Transcranial Doppler

CLINICAL MANIFESTATIONS OF IRON OVERLOAD


Transfusional Excess Iron Can Build Up in Key Organs

Liver

Physiology of Iron Overload

Outcome = Tissue Iron x Tissue Sensitivity x Time

- Iron Input
- Total Iron (LIC)
- Tissue Iron
- Iron Accumulation in Organs
- Organ Dysfunction

LIVER DISEASE

- Primary Iron storage organ. Involvement is early & frequent: 38-97%
- Asymptomatic
- Liver enlargement
- Elevated Serum Aminotransferase levels
- Hepatic Fibrosis: 10-25%
- Cirrhosis: 4-6%
- Contributing factors: HFE, Alcohol, HCV

CARDIOTOXICITY

- Of all the organs, the myocardium is most sensitive to iron toxicity. Major mortality
- From Asymptomatic to sudden death
- Left Ventricular diastolic Dysfunction
- Cardiomyopathy: Both Dilated & Restrictive. Impaired Systolic Function and Heart Failure
- “Malignant” Arrythmias: Sick sinus synrd. & Atrial FIB

ENDOCRINE DISEASE: DIABETES & HYPOGONADISM

- DM: Decrease Insulin secretion due to accumulation of Iron in Beta Islet cells of Pancreas &/or Increased Insulin Resistance
- Hypogonadism: Hypothalamic, Pituitary and gonadal dysfunction.
- Thyroid dysfunction: Less common. Hypo/Hyper Thyroidism
JOINT & SKIN

- Arthropathy: 25-50% of cases. A predilection for the 2nd & 3rd Metacarpophalaneal joints (MCP’s). Other joints usually symmetrical
- Osteoporosis
- Skin: Hyper pigmentation: Results from melanin &/or Iron deposition. Skin appears brownish "bronze"

MANAGEMENT OF TRANSFUSIONAL IRON OVERLOAD
DIAGNOSIS, PREVENTION & TREATMENT

ASSESSMENT OF IRON LOAD

- Serum Ferritin (SF)
- SQUID: Super Conducting Quantum Interference Device. Few & largely replaced by MRI
- MRI assessment of Liver iron(R2). Based on measurements of proton transverse relaxation rates
- MRI assessment of Cardiac iron (T2*)
- Liver Biopsy: ? Still Gold Standard

Factors for Consideration

- When selecting a measure for iron levels, consider the following
  - Clinical value
  - Availability
  - Cost
  - Accuracy
  - Invasiveness
  - Patient concerns

Iron Overload: Relationship Between Hepatic Iron and Transfusion Duration in Patients With SCD

Serum Ferritin as a Measure of Iron Loading

- Reflects
  - Iron stores
  - Inflammation
  - Recent chelation
  - Ascorbate status

Hepatic Iron Stores and Serum Ferritin

- Sickle cell anemia (n = 50)
- Thalassemia major (n = 74)
Serum Ferritin: Advantages

- Inexpensive and widely available
- Noninvasive
- Grossly proportional to total body iron load in large population studies
  - Correlations ~0.7 with biopsy or surrogates
- The direction and magnitude of change in serum ferritin are reasonable markers of the direction and magnitude of change in iron burden

Serum Ferritin: Disadvantages

- Is a poor measure of total iron burden in individual patients
- Increased with inflammation
- Decreased if scorbutic
- Effect of chelation not linear
- Different chelators may affect serum ferritin differently

LIC Predicts Total Body Iron

\[
\text{Body iron (mg/kg)} = 10.6 \times \text{LIC (mg/g dry weight)}
\]

Liver Biopsy

- Liver biopsy
  - Distribution artifact
  - Risks of procedure
  - Patient acceptance
  - Adequate sample size
    - >1 mg dry weight
  - LIC >7 mg/g dry weight is generally considered an indicator of iron overload

Histology of Iron Overload

- Excess iron is deposited in tissues (hemosiderosis)

MRI R2

- Can accurately estimate iron in liver
- Noninvasive and MRI instruments are widely available
- Validated by preliminary clinical research on MRI machines from several manufacturers at several institutions, in patients with transfusional iron overload
- MRI machine must be calibrated to measure iron
Transfusional Excess Iron Can Build Up in Key Organs

MRI of an iron-overloaded human liver

1 Bright areas indicate high iron concentrations, while the dark areas indicate regions of lower iron concentrations.
MRI = magnetic resonance imaging

HEPATIC IRON & SEVERITY

<table>
<thead>
<tr>
<th>HEPATIC IRON (mg/g Dry Weight)</th>
<th>SEVERITY</th>
<th>CLINICAL IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.2</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>3-7</td>
<td>Mild</td>
<td>Optimal level</td>
</tr>
<tr>
<td>7-15</td>
<td>Moderate</td>
<td>Increased Risk of Complications</td>
</tr>
<tr>
<td>&gt;15</td>
<td>Severe</td>
<td>Increased Risk of Cardiac disease &amp; Sudden death</td>
</tr>
</tbody>
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Ho et al: Australian Guidelines for the assessment of Iron overload & iron chelation 2011

ASSESSMENT OF CARDIAC RISK BY MRI

<table>
<thead>
<tr>
<th>Cardiac T2* (ms)</th>
<th>Cardiac Iron Load &amp; Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20</td>
<td>Normal</td>
</tr>
<tr>
<td>Cardiac T2* (ms)</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>10</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Ho et al: Australian Guidelines for the assessment of Iron overload & iron chelation 2011

CHELATORS

- DEFEROXAMINE: Available in the 60’s. Widely used after 1975. Parenteral SQ/IV
- Novel Iron chelator, FBS 0701 just completed Phase 2 trials: Ellis Neufeld et al; Blood 2012 119 3263-3268

Search for the “holy grail” of chelators continues: Comparison

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>IDEAL CHELATOR</th>
<th>DEFEROXAMINE</th>
<th>DEFERASIROX</th>
<th>DEFERIPRONE</th>
<th>DEFERASIPROX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROUTE</td>
<td>ORAL SQ/IV</td>
<td>ORAL</td>
<td>ORAL</td>
<td>ORAL</td>
<td>ORAL</td>
</tr>
<tr>
<td>HALF-LIFE</td>
<td>Long enough to give constant protection from labile Fe</td>
<td>Short (min)</td>
<td>Moderate (&lt;2hrs)</td>
<td>Long (8-16 hr) Dose QD</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>None</td>
<td>Pain/Local inflammation</td>
<td>Agranulocytosis</td>
<td>GI, Rash</td>
<td>Increase Cr.</td>
</tr>
<tr>
<td>ABILITY TO CHELATE</td>
<td>High</td>
<td>? Lower than oral agents</td>
<td>High</td>
<td>Not shown to be great</td>
<td></td>
</tr>
<tr>
<td>CARDIAC &amp; TISSUE Fe</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Ellis Neufeld et al; Blood 2012 119 3263-3268
Summary & Recommendations

- Desferoxamine has been available for decades and has the longest cumulative evidence. Still recommended for severe cardiac overload IV continuous.
- Combinations of DFO & Deferiprone are widely used for moderate cardiac toxicity.
- Other agents as ACE inhibitors & Beta blockers have not been adequately studied in this setting and do not replace chelation.
- Advances in imaging (MRI) allow titration of Rx to organ Iron load.

Iron Balance

- Considerations:
  - Transfusional burden
  - Accuracy of patient reporting
  - Patient-specific differences in chelation efficacy

ON A PERSONAL NOTE & CALL TO ACTION

THANK YOU
QUESTIONS & ANSWERS