Sickle Cell Disease: Stroke and Other Complications

Hematology Fellows Conference
July 13, 2012
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Pediatric and Adult Hematology
Disclosures

• I have nothing to disclose.

• Objectives
  • Recognize the stroke and other central nervous system complications of SCD
  • Describe the evaluation of fever in people with SCD
  • Describe the basic management of complications of SCD
Outline

- Sickle Cell Basics
- Fever/Infection
- Priapism
- Biliary tract disease
- Stroke
- Acute Anemic Episodes
- Changes in Vision
Median Life Expectancy (Years)

Sickle Cell Research for Treatment and Cure, NIH, NHLBI, DHHS, 2002.
Genotypes

- Sickle Cell Anemia (HbSS)
  - Most common (60-65%)
  - On average most severe
- Sickle C disease (HbSC)
  - Less common (20-30%)
  - More mild disease
- Sickle-β null thalassemia (HbSβ0)
- Sickle-β plus thalassemia (HbSβ+)
Predicting Severity in HbSS

- Definitions of severe disease
  - Death or stroke
  - Frequent hospitalization for severe pain
  - Frequent acute chest syndrome

- Influenced by improvements in care
  - Prevention of infection
  - Empiric treatment and supportive care
Predicting Severity

The Old
- Dactylitis < 1 year
- In 2nd year of life
  - Hb < 7 g/dl
  - WBC >20,000/ul
- Alpha thalassemia

The New
- WBC >20,000/ul
- Network Models
  - Blood transfusion
  - ↑ Bilirubin
  - ↑ Reticulocytes
  - ↑ WBC
  - ↑ MCV
- Male sex
- Asthma

Asthma

- Similar prevalence in SCD (~20%)
- Associated with increased rate of
  - Admission for pain (200% increase)
  - Acute chest syndrome (100% increase)
  - Transfusion (60% increase)

Sickle Cell Mutation (stripes) and Malaria (green)
Case Identification

- Newborn screening: all 50 states and D.C.
- SCD in 1 in 2500 newborns
  - 1 in 346 African-Americans
  - Started in 1987 after penicillin prophylaxis study
- Increasing at risk populations in U.S.
  - Hispanic children
  - Arab, Turkish and Indian immigrants
  - African immigrants not screened at birth

http://www.cdc.gov/genomics/training/books/21stcent4a.htm#Chapter22
## Prevent Infections

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinations</td>
<td>Prevnar-13, Influenza, HIB, Pneumovax, Menactra</td>
<td>Influenza, Pneumovax</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Penicillin 125/250 BID</td>
<td>RarelyUsed</td>
</tr>
<tr>
<td>Avoid exposures</td>
<td>Reptiles, amphibians Influenza vaccination for family members</td>
<td>Same</td>
</tr>
</tbody>
</table>
### Cases of Invasive Pneumococcus per 100,000 Person-Years

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-Prevnar 1995-99</th>
<th>Post 2001-04</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years</td>
<td>3630</td>
<td>335</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>2044</td>
<td>134</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>161</td>
<td>99</td>
</tr>
</tbody>
</table>
Pneumococcus Returns!

Influenza

• Greatly increased risk of hospitalization
  • For SCD 56 times that of children <18 years
  • Similar severity to other hospitalized children
• Proportion with ACS and admitted to ICU
  • Seasonal influenza A or B 13% 3%
  • Epidemic H1N1 influenza 34% 17%
• H1N1 more severe and 8% hospitalized

Fever

- Emergent evaluation of fever $\geq 101.5^\circ$
  - CBC with differential, retic, blood culture
  - Urinalysis, urine culture
  - Chest x-ray
- Empiric intravenous antibiotics
- Hospitalization if $< 3$ years of age
  - Unable to reliably return to hospital
  - High risk clinical features
Priapism

- Prolonged painful erections
- Seek medical attention if ≥ 2 hours
- Frequency increases with puberty
- Prevention
  - Decrease endogenous androgens
  - Other therapies unproven
  - On-going study of daily sildenafil
Priapism

• Home management
  • Empty bladder
  • Analgesics
  • Hydration
  • Gentle exercise

• Hospital management
  • IV hydration and analgesics
  • Aspiration and irrigation if prolonged
  • Surgical shunting if refractory
Biliary Tract Disease

- Cholelithiasis
  - Pigment stones >50% with HbSS and 20% with HbSC by 23 years of age
  - Risk of stone correlated with total bilirubin
  - Cholecystectomy only if symptomatic

- Acute cholecystitis
  - Pre-operative transfusion
  - Recommend admission even after elective uncomplicated laparoscopic cholecystectomy
Biliary Tract Disease

- Common bile duct obstruction
  - Frequent at presentation of cholecystitis
  - Recommend ERCP, cholecystectomy
  - Occasional patients have frequent recurrences

Large stone obstructing the common bile duct at the head of the pancreas
CNS COMPLICATIONS OF SCD

NORMAL

COGNITIVE DEFICITS

SILENT INFARCT

STROKE

ICH/SAH

DEATH
Age of First CVA by Hb Genotype

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Risk factor</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
<th>Participants</th>
<th>Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houston et al. (1997)</td>
<td>Homocysteine (&gt; median)</td>
<td>3.5 (1.1–12)</td>
<td>0.03</td>
<td>16 with stroke 83 without stroke</td>
<td>50% adults, corrected for age, stroke type not specified</td>
<td>[66]</td>
</tr>
<tr>
<td>Miller et al. (2001)</td>
<td>Silent cerebral infarct</td>
<td>14</td>
<td>0.006</td>
<td>248 children</td>
<td>Infant cohort of the CSSCD</td>
<td>[67]</td>
</tr>
</tbody>
</table>

| Prior TIA    | 56 (12–285)                    | <0.001              | 2436 children and adults with HbSS |
| Steady-state Hb (per g/dl) | 1.9 (1.3–2.6) | <0.001              |
| ACS within 2 weeks | 7 (1.8–27)         | 0.001               |
| ACS rate (event/year) | 2.4 (1.3–4.5) | 0.005               |
| SBP (10 mm increase) | 1.3 (1.03–1.7) | 0.033               |

| Hypertension | 4.1 (2.9–5.7) | <0.0001              | 255 acute strokes |
| Diabetes mellitus | 2.2 (1.2–3.9) | <0.05               | among 69,586 |
| Hyperlipidemia | 6.9 (2.9–14)   | <0.0001              | discharges with |
| Renal disease | 4.2 (2.4–6.8) | <0.0001              | diagnosis of sickle cell disease |
| Atrial fibrillation | 4.9 (2.2–9.5) | <0.0005              |

ACSA: Anterior cerebral artery; ACS: Acute chest syndrome; CBV: Cerebral blood flow velocity; CSSCD: Cooperative Study of Sickle Cell Disease; dICA: Distal internal carotid artery; Hb: Hemoglobin; HbSS: Sickle cell anemia; MCA: Middle cerebral artery; SaO2: Oxygen saturation; SBP: Systolic blood pressure; STOP: Stroke Prevention Study; TCD: Transcranial Doppler ultrasound; TIA: Transient ischemic attack.
### Risk Factors for Hemorrhagic Stroke

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady-state Hb (for every 1 g/dl decrease)</td>
<td>1.6 (1.1–2.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Steady-state leukocyte count for every 5000/µl increase</td>
<td>1.9 (1.7–2.2)</td>
<td>0.026</td>
</tr>
<tr>
<td>Hypertension</td>
<td>NC (1.7–NC)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Events in the last 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion of RBCs</td>
<td>35 (4.9–289)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>20 (2.9–217)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4.4 (0.9–21)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Transfusion in last 14 days</td>
<td>15 (1.5–708)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.7 (4.7–13)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>7.2 (3.4–14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>9.1 (2.8–23)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.3 (0.9–13)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Stroke Prevention

- Ischemic stroke in children
  - Screen with transcranial Doppler US to identify high risk group (10%/year)
  - Transfusions every 4 weeks
    - Reduces risk of stroke to 1%/year
    - Duration of transfusion-30 months inadequate
- No data in adults
- Hemorrhagic stroke-? Careful transfusion

Adams et al. NEJM 1998;339:5-11
Adams et al. NEJM 2005;353:2769-78
Time Averaged Maximal Velocities of >200 cm/sec in the distal internal carotid or middle cerebral arteries
Adult Survival by Type of Stroke

- Ischemic Stroke
- Primary Hemorrhagic Stroke

$p=0.05$ Log-Rank Test
Acute Treatment of Stroke

• Hemorrhagic and ischemic
  • Complete evaluation for typical causes
    • Consult neurology or stroke service
  • Exchange transfusion to reduce HbS <30%
    • Established therapies in the general population
• SAH- embolization or clipping if aneurysm
• Ischemic-Consider TPA if meets guidelines, ASA

Secondary Prevention of Stroke

- Hemorrhagic
  - Treatment of modifiable risk factors
  - Role of transfusions or hydroxyurea unclear

- Ischemic
  - Regular transfusions to maintain HbS <30-50%
    - Decreased stroke: 67% at 4 years to 2.1/100 person-years
    - 45% had progressive cerebral infaracts after 5.5 years
  - Treatment of modifiable risk factors
  - Alternatives- hydroxyurea, HSCT, revascularization

Hulbert et al. Blood 2011;117(3):772-77
Silent Cerebral Infarct

- Frequent complication of SCD
  - Ischemic changes on MRI without history or physical exam consistent with stroke
  - From 16 – 30% of children with HbSS
- Associated with increased risk of
  - Cognitive impairment
  - School failure
  - Overt Stroke

Schatz et. al. Neurology 56:1109-11.
Silent Cerebral Infarct

<table>
<thead>
<tr>
<th>Complication</th>
<th>Peds</th>
<th>Adult</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic CVA</td>
<td>0.21</td>
<td>0.30</td>
<td>26% death</td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>0.51</td>
<td>0.19</td>
<td>0% death</td>
</tr>
<tr>
<td>Silent Infarct-1st</td>
<td>1.01</td>
<td>14%</td>
<td>Lower IQ</td>
</tr>
<tr>
<td>2nd/Progressive Prevalence</td>
<td>7.06</td>
<td>ND</td>
<td>School failure 58%</td>
</tr>
<tr>
<td>Cog deficits (controls)</td>
<td>11%</td>
<td>15%</td>
<td>Visual-motor</td>
</tr>
<tr>
<td>HbSS nl MRI</td>
<td>27%</td>
<td>33%</td>
<td>&amp; spatial</td>
</tr>
<tr>
<td>HbSS SCI</td>
<td>79%</td>
<td>ND</td>
<td>Attention/EF</td>
</tr>
</tbody>
</table>

Cognitive Deficits in Adult

- Not very well characterized
- Rigorous study of people with HbSS
  - Excluded those with known stroke
  - Slow processing speed 87(HbSS) 99 (controls)
  - Performance IQ 90.6 95.9
  - Age related decline in PIQ in those with Hb <7.6

Vinchinsky et al. JAMA 2010;303:1823-1831
Acute Anemic Episodes

- Hyperhemolysis
  - Occurs frequently with vaso-occlusion
  - Hemoglobin drops 1 to 2 g/dl
- Splenic sequestration
- Decreased production
  - Diagnose by CBC and reticulocyte count
Acute Splenic Sequestration

- HbSS <5 years old
- HbSC, HbSβ⁺ thalassemia >5 years old

Symptoms/Signs
- Irritability
- Weak
- Pale
- Tachycardia
- Lethargy
- LUQ pain
- Splenomegaly

Labs
Acute Splenic Sequestration

- Uncommon in adults

- Treatment
  - Acutely-transfusion with care
  - Chronically-transfusions, splenectomy

- Chronic splenomegaly
  - May cause thrombocytopenia, anemia
  - Splenectomy if symptomatic.
Aplastic Crisis

- Severe anemia
- ↓↓ reticulocytes
  - Fifth disease
  - Parvovirus B19
  - Lasts 10-14 days
  - Very contagious
- Often need blood transfusion
- Can miss in HbSC
Aplastic Crisis

- Parvovirus infection mostly in children
  - 70% seropositive by age 20
- Associated with
  - Stroke
  - Acute chest syndrome
  - Glomerulonephritis
  - Multiorgan failure syndrome

Multiorgan Failure Syndrome

- Lung - new infiltrate with >3 L/min of O₂
- Liver - ALT, total bili >5x, direct bilirubin >2 x nl & baseline, PT >3 sec prolonged
- Kidney - acute injury - creatinine > 2 mg/dl
- Need 2 of 3 organs, at least 2 for liver
- Occurs after acute sickle cell pain
- Seen in all genotypes

Possible Mechanism

SICKLING → MICROVASCULAR OCCLUSION → PAIN

HYPOXEMIA → INCREASING ANEMIA → FAT EMBOLI

INFECTION → DIFFUSE TISSUE ISCHEMIA

DIFFUSE TISSUE ISCHEMIA → ACUTE MULTIORGAN FAILURE → DEATH

TRANSFUSION → ACUTE MULTIORGAN FAILURE
Acute Loss of Vision

- Proliferative sickle retinopathy
  - More common in HbSC (36%) than HbSS (12%)
  - Causes vitreous hemorrhage and retinal detachment
- Retinal artery occlusion
  - Often in young patients
- Glaucoma
  - After traumatic hyphema in SCD and trait
  - Caused by occlusion of trabecular network
Multiple occluded arterioles surrounding the foveal avascular zone and inferior/inferonasal to optic nerve.
Take Home Points

• Treat pain at home and after evaluation
• Prevent and treat of infection in primary care and acute settings
• Recognize and treat severe acute complications of SCD with transfusion