Medical Knowledge Fiesta 2012

Sickle Cell Disease: Current Management

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RBC Morphology

A. Normal red cell
B. Sickled red cell

Scanning Electron Micrographs

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Sickle Cell Disease

Origins and Distribution
Genetics of Hemoglobinopathies

Human Hemoglobin Genes and Products

- **Chromosome 16**
  - **Globin proteins**
  - "Embryonic"
  - "Fetal"
  - "Minor adult"
  - "Major adult"

- **Chromosome 11**
  - **Globin proteins**

**α-globin gene family**

**β-globin gene family**

**Hemoglobins: Birth**
- **F**: $\alpha_2 \gamma_2$ 60-90% < 2%
- **A2**: $\alpha_2 \delta_2$ < 1% 2-3%
- **A**: $\alpha_2 \beta_2$ 10-40% 96%

> 1 yr

**Sickle Cell Foundation of Ghana**
Molecular Origins of Sickle Cell Disease

Polymorphic Sites in β-Gene Complex Confirm Multicentric Origins of βs Mutation

1. Senegal
2. Benin
3. Bantu
4. Cameroon
5. India/Saudi

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Genetics of Sickle Cell Disease

The $\beta^s$ Mutation

6th Codon of $\beta$-Globin Gene

GAG $\rightarrow$ GTG

Glutamic acid $\rightarrow$ Valine

The same mutation found in all $\beta^s$ genes around the world
Sickle Cell Disease
Sickle Gene Travels the Globe

Origins (2000-1000 BC?):
- West, Central Africa
- India/E. Saudi Arabia

Early migration: (200-1000 BC)
- North Africa
- Mediterranean
- Middle East

Later migration: (1500-1900)
- Americas
- Europe

Modern migration: Global

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Diagnosis of Sickle Cell Disease

Laboratory Tests

1. Blood smear
2. Slide sickling preparation
3. Solubility test
4. Complete Blood Count, reticulocyte count
5. Hemoglobin separation tests
6. Quantitation of hemoglobin fractions
7. Quantitation of globin chain fractions
8. DNA-based tests
9. Family studies
1. Blood Smear

• Typical sickled cells not evident on blood smears of all patients, especially not on smears of young children and others with high Hb F.

• May be helpful when other diagnostic tests are not available
Diagnosis of Sickle Cell Disease

2, 3. “Sickling” Tests for Hb S

- Of no use as a primary screening tests
- Positive = Presence of Hb S
- Negative in newborns, infants and others with high levels of Hb F; negative for Hb C
- Does not distinguish sickle cell trait (AS) from types of SCD
- In emergency, may help raise suspicion of SCD
- Can help distinguish Hb S from other hemoglobins with similar electrophoretic migration or chromatographic retention patterns.
Diagnosis of Sickle Cell Disease

4. Complete blood count (with reticulocyte count)

- Never diagnostic by itself

- Degree of anemia and reticulocytosis helps define types of SCD when other methods are not specific.

  Note: SCD variants such as SCD-SC, SCD-Sβ+ thal, and SCD-S(δβ)ο thal may have mild or no anemia.

- Mean Cell Volume (MCV) and Mean Cell Hemoglobin (MCH), when low suggest presence of thalassemia - alpha and/or beta.
Diagnosis of Sickle Cell Disease

4. The reticulocyte

New methylene blue stain                  Wright-Giemsa stain

Source of reticulum: remnants of ribosomal RNA from protein synthesis
Diagnosis of Sickle Cell Disease

5. Hemoglobin Separation Methods

Most common tests used in clinical laboratories

a. Hemoglobin Electrophoresis
   - Cellulose acetate at alkali pH (manual)
   - Citrate agar gel at acid pH (manual)
   - Capillary electrophoresis (automated, quantitative)

b. Isoelectric focusing (IEF) (manual)

c. Chromatography
   - High-performance liquid chromatography (HPLC)
     (automated, quantitative)

There are > 1,100 variants of the 3 normal hemoglobins, A, A2, and F; they cannot all be separated by any of these methods
Diagnosis of Sickle Cell Disease

5a. Hemoglobin Electrophoresis

Cellulose acetate, pH 8.6
Sickle Cell Disease

Variants
# Common Variants of Sickle Cell Disease

<table>
<thead>
<tr>
<th>Variant</th>
<th>Hbs in RBC</th>
<th>Clinical Course</th>
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<tbody>
<tr>
<td>SCD-SS</td>
<td>( F_S )</td>
<td>( S_{FA2} )</td>
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Diagnosis of Sickle Cell Disease

A newborn with abnormal screening results:

Possible Genotypes for FS:
- SCD-SS (severe)
- SCD-S$\beta^o$ (severe)
- SCD-S($\delta\beta$)$^o$ (very mild)
- S-HPFH (asymptomatic) (hereditary persistence of fetal Hb)

FS $\rightarrow$ FSA$_2$ $\rightarrow$ SFA$_2$ $\rightarrow$ SA$_2$F
Sickle Cell Disease

Inheritance
Genetics of Sickle Cell Disease

When both parents have Sickle Cell Trait (AS)

Each and every time they make a baby…

(AA)  (AS)  (AS)  (SS)
Genetics of Sickle Cell Disease

When one parent has AS and the other has $\beta^0$-thal Trait (beta-zero thalassaemia trait)

This parent has no S ("sickling" negative)

Sickle beta-zero thalassaemia (S$\beta^0$-thal)
Pathophysiology of Sickle Cell Disease

Clinical Pathology

1. Anemia
2. Vasoocclusion
3. Chronic organ damage

Wide range of secondary effects; and, wide variability in clinical expression
Pathophysiology of Sickle Cell Disease

Clinical Pathology

1. Anemia

- chronic intravascular and extravascular hemolytic anemia
- acute anemia
  - transient red cell aplasia (parvovirus B19)
  - acute splenic sequestration
  - infection-related acute hemolysis
Clinical Pathology

2. Vasoocclusive complications

A. Microvascular occlusion
   • clinically silent

B. Macrovascular occlusion
   • acute ischemic/infarctive damage
     • pain episodes (tissue ischemia/infarction)
     • stroke
     • priapism
     • acute chest syndrome
     • renal papillary necrosis
     • splenic infarction
SCD: Dactylitis ("hand-foot syndrome")
SCD: Acute chest syndrome (Day 1)
SCD: Acute chest syndrome (Day 4)
Stroke

Residual: Left hemiparesis, slurred speech
Stroke
Magnetic Resonance Angiography (MRA)
Sickle Cell Disease: Clinical Pathology

7-year old: MRA 6 months prior to stroke

Stroke
Sickle Cell Disease: Clinical Pathology

Stroke

MRI/MRA

Residual: Left hemiparesis, slurred speech
Stroke in Sickle Cell Disease

Silent Infarct in 6 y.o. with SCD-SS
Clinical Pathology

3. Chronic organ damage

- splenic dysfunction
  - high risk of bacterial/malarial infection
- progressive dysfunction of
  - brain - silent infarcts, neurocognitive dysfunction
  - eyes - retinopathy
  - lungs - restrictive, pulmonary hypertension
  - heart - cardiac failure
  - kidneys - hyposthenuria, proteinuria, renal failure
  - liver and gallbladder – gallstones, cholangitis
  - joints - avascular necrosis
Development of Functional Asplenia

Infant with SCD-SS

Age 3 months

$^{99}$Tc Sulfur colloid Liver-Spleen Scan
Sickle Cell Disease: Clinical Pathology

Development of Functional Asplenia

Infant with SCD-SS

Age 3 months

Age 8 months

$^{99}$Tc Sulfur colloid Liver-Spleen Scan
Sickle Cell Disease

Treatment
Management of SCD: Tools

General:

- Antimicrobials – antibiotics, anti-malarials
- Anti-pneumococcal vaccination
- Analgesics
- Fluids
- Respiratory support
- Surgical interventions
- Psychosocial support and interventions

Specific:

- Blood (RBC) transfusion
- Hydroxyurea therapy
- Hematopoietic stem cell transplantation
- Gene therapy
Management of SCD in Adults

Health Maintenance

Prevention of Invasive Pneumococcal Disease
Immunizations

Screening:
- Renal Disease
- Pulmonary Hypertension
- Electrocardiography
- Hypertension
- Retinopathy
- Risk of Stroke Using Neuroimaging

Respiratory Disorders in SCD

Reproductive Counseling and Contraception

General Preventive Health Recommendations
Management of SCD

Disparities in Sickle Cell Disease Services

10 Major Services NOT Universally Available

1. Newborn screening followed by penicillin prophylaxis and anti-pneumococcal vaccination

2. Management of children with signs of infection

3. Modern pain management

4. Stroke prevention strategies: TCD, MRI and MRA

5. Regular red cell transfusion service

6. Hydroxyurea therapy

7. Neuropsychological dysfunction - diagnosis and management

8. Hematopoietic stem cell transplantation

9. Pulmonary hypertension - diagnosis and management

10. Premarital, pre-pregnancy, pre-natal testing, and counseling
Management of SCD

Disease Modifying Therapies

• Blood (RBC) transfusion
• Hydroxyurea therapy
• Hematopoietic stem cell transplantation
• Gene therapy
Thank you