Lecture 14

Sickle Cell Anemia

November 8, 2002

**Learning Objectives**

- Understand the molecular basis of sickle cell anemia and how to make a diagnosis
- Begin to recognize the clinical features sickle cell anemia
- Know that Hgb S is a balanced polymorphism, and understand the meaning of a haplotype.
- Know the conditions that facilitate sickling
- Understand why patients with sickle cell who co-inherit thalassemia trait will have a milder course
Qualitative Abnormalities of Hemoglobin

- Silent Variants
- Unstable hemoglobins
  - Heinz body hemolytic anemia
- Methemoglobinemia
- High affinity hemoglobins
  - polycythemia (↑hematocrit and hemoglobin)
- Low affinity hemoglobins
  - mild anemia (↓hematocrit and hemoglobin)
- Hemoglobin S
- Hemoglobin C

Textbook Figure 6.6
Figure 6.7. The DNA and protein abnormalities in codon 6, which lead to sickle hemoglobin (β^s) and hemoglobin C (β^c).
Cellulose acetate electrophoretic patterns for common hemoglobinopathies

from the Red Cell Manual
### Table 10-11. FREQUENCY OF HEMOGLOBIN GENOTYPES AMONG BLACK AMERICANS

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*</td>
</tr>
<tr>
<td>AS</td>
<td>8.6</td>
</tr>
<tr>
<td>SS</td>
<td>0.14</td>
</tr>
<tr>
<td>AC</td>
<td>2.4</td>
</tr>
<tr>
<td>CC</td>
<td>0.02</td>
</tr>
<tr>
<td>SC</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Survey of 250,000 black Americans\(^{356}\)

**Review of literature\(^{357}\)

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**Diagnosis of the sickle mutation using Southern blot analysis**

Textbook Figure 6.10
Table 10-10: EFFECT OF α-THALASSEMA ON THE PERCENTAGE OF β-CHAIN VARIANT HEMOGLOBIN IN HETEROZYGOTES

<table>
<thead>
<tr>
<th></th>
<th>AS (Ref)</th>
<th>Percentage of Variant in HemoIysate</th>
<th>AC (Ref)</th>
<th>AE (Ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (α+α+)</td>
<td>41 ± 1.8 (632)</td>
<td>43.8 ± 1.5 (631)</td>
<td>30 ± 1.5 (662)</td>
<td></td>
</tr>
<tr>
<td>α/α−</td>
<td>35.4 ± 1.0 (631)</td>
<td>37.8 ± 1.4 (631)</td>
<td>27 ± 2 (662)</td>
<td></td>
</tr>
<tr>
<td>α/α− or α−/α−</td>
<td>26.1 ± 1.4 (631)</td>
<td>32.2 ± 0.8 (631)</td>
<td>22 ± 2 (662)</td>
<td></td>
</tr>
<tr>
<td>α− (Hb H)</td>
<td>17 (632)</td>
<td>15 (668)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron deficiency*</td>
<td>30±42 (633)</td>
<td>18±27 (666)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Before and after correction
Hb S only occurs on 4 haplotypes…only occurred 4 times in history

One single mutation in history accounts for Hb C
Hb S is a balanced polymorphism

* homozygotes (1 in 500) are selected against
* heterozygotes (1 in 12) are selected for
Complications of Sickle Cell Anemia

- autosplenectomy
- hyposplenuria
- Infections
  - encapsulated organisms: pneumococcus
  - salmonella, staph
- Painful crises
- Bone infarcts, aseptic necrosis
- Stroke
- Acute chest syndrome
- Hand-foot syndrome
- Chronic organ damage
% of SS and SC patients developing retinopathy
Table 12-6. CAUSES OF DEATH AMONG CHILDREN WITH SICKLE CELL DISEASE*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage of Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>44</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>16</td>
</tr>
<tr>
<td>Sudden, unexpected death</td>
<td>14</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>12</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>


![Graph showing the percentage of patients with low morbidity, moderate-to-high morbidity, chronic organ failure, and death over age (years).](image)
Sickle Cell Anemia: Treatment

- IV fluids
- Analgesia
- Infection
  - penicillin prophylaxis
  - vaccines
- Oxygen
- Transfusion
- Butyrate
- Hydroxyurea
- Bone Marrow Transplantation

Bone Marrow Before therapy

During therapy

Reduced cellularity
Increased proportion of nucleated red cells
Producing hemoglobin F

Blood Before therapy

During therapy

Increased hemoglobin F
Macrocytosis
Increased hydration
Fewer sickled cells
Fewer reticuloocytes
Fewer granulocytes

Vasculature Before therapy

During therapy

Reduced adherence
Improved endothelial function
Summary

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