Sickle-Cell Anemia:
When Good Red Blood Cells Go Bad

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What is sickle-cell anemia?

- It is a genetic disease where red blood cells have a sickled shape.

What is the cause of the disease?

- It is caused by a single amino acid substitution in the B-chain of hemoglobin (Hb).
- GAG (6-glutamic acid) is converted to GTG (valine).
- Hb is the O_2 carrying molecule found in RBC's.

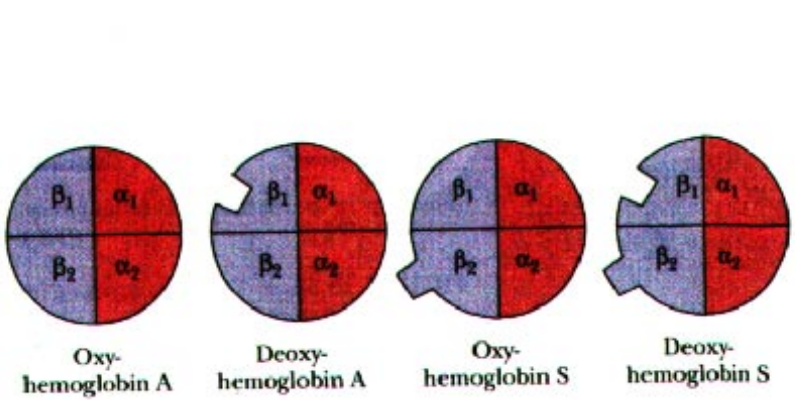
What is the cause of the disease?

- Amino acid residues at B-6 are found on the surface of the molecule.
- In normal hemoglobin (HbA), the ionic R-group of glutamic acid fits into this environment.
- In sickle cell hemoglobin (HbS), the aliphatic side chain of the valine residue creates a protrusion where none existed before.
- When there is O_2, the two types of hemoglobin behave in almost the same way.

What is the cause of the disease?

- When there is a low level of O_2, deoxyhemoglobin forms and HbA molecules remain in solution, but HbS molecules come out of solution and a crystal-like solid forms.
- The solids form when neighboring HbS molecules polymerize (aggregate together).

The polymerization of HbS



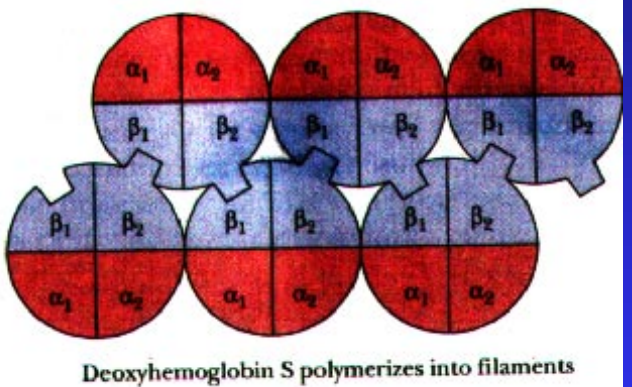


FIGURE 15.40 • The polymerization of Hb S via the interactions between the hydrophobic Val side chains at position $\beta 6$ and the hydrophobic pockets in the EF corners of β-chains in neighboring Hb molecules. The protruding "block" on Oxy S represents the Val hydrophobic protrusion. The complementary hydrophobic pocket in the EF corner of the β-chains is represented by a square-shaped indentation. (This indentation is probably present in Hb A also.) Only the β_2 Val protrusions and the β_1 EF pockets are shown. (The β_1 Val protrusions and the β_2 EF pockets are not involved, although they are present.)

What is the cause of the disease?

- The aggregations cause the sickled shape of the cells to form.
- These cells can get caught in small blood vessels, and clots form.
- When clots form in deep tissues, less O_2 is available and as a result more deoxyhemoglobin forms.

What is the cause of the disease?

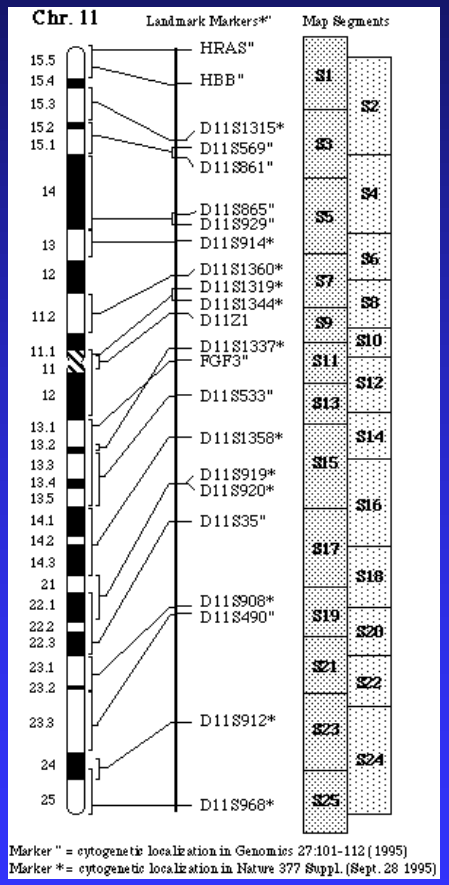
- Then, due to the higher level of the deoxyhemoglobin more aggregates form and the clot gets bigger.
- This is a vicious cycle that keeps repeating itself.

Types of sickle cells

- There are two types of sickle cells.
  - Reversible
  - Irreversible
- In a reversible sickle cell, the polymer dissolves and the cell goes back to its normal function.
- After many episodes, the cell becomes irreversibly sickled and won't resume its normal shape even when it is re-dissolved.

Gene's Location

- The gene that encodes for the B-chains of the Hb molecule is located on chromosome 11 at position 11p15.5.



Who has sickle cell anemia?

- Sickle cell anemia is an autosomal recessive disease.
- 1/500 African Americans have the disease. (They have two copies of the sickle cell gene.)
- 1/12 African Americans are carriers of the disease. (They have one copy of the sickle cell gene.)

Why is it found in this population?

- The disease malaria, which is carried by mosquitoes, is found in large areas of Africa.
- People who have one copy of the gene, carriers, have less severe effects when they get malaria.
- RBC's that contain malaria parasites are approximately 0.5pH lower (have more H^+).

Why is it found in this population?

- This stabilizes the deoxystate of Hb.
- As a result:
  - The RBC will blow up before the malaria matures.
  - It encourages the sickling of RBC's with malaria, and they are taken out of circulation by the spleen.

Symptoms

- Painful episodes:
  - Most pain occurs when sickled cells block small blood vessels, and parts of the body don't get enough O_2.
  - When body parts are deprived of O_2, they release chemicals that cause the pain.
  - Where tissue is damaged the area can become inflamed, which causes more pain.

Symptoms

- The pain most commonly occurs in the bones, chest, and abdomen.
- It usually lasts a few days, but it can last for weeks at a time.

Symptoms

- Bones:
  - Bone marrow is active in people with sickle cell anemia, so that destroyed blood cells can be replaced.
  - The blood must travel through sinusoids in spongy bone, and inflexible sickle cells can get trapped in them causing a blockage in circulation and causing pain.

Symptoms

- Hand-foot syndrome is common, and is often seen in young infants and children.
  - Symptoms are pain, low-grade fever, and edema of the hands and feet, which extends to the fingers and toes.

Symptoms

- Chest:
  - Patients often have a narrower chest and their heart is larger. This leaves the lungs less room to work, and therefore they get less oxygen.
  - Acute chest syndrome can occur when a person's lungs undergo blood vessel blockage, or become infected.
    - These patients must be admitted to the hospital for treatment.

Symptoms

- Abdomen:
  - Blockage of blood vessels serving the abdominal region can cause pain, which lasts for four to five days.
  - Especially vulnerable are the liver and spleen.

Symptoms

- In the liver, blood cells can become trapped causing injuries and scarring.
- In the spleen, blood cells can get trapped, which causes the spleen to swell and not function properly.
  - As a result, it doesn't produce antibodies as well and patients are more vulnerable to infection.

Symptoms

- Gallstones:
  - A product of RBC's is bilirubin, a pigment that is excreted by the liver into the bile.
  - Because so many RBC's are destroyed, bilirubin is produced in a high amount and as a result gallstones form.

Symptoms

- Leg ulcers:
  - They occur between the ages of 10-50.
  - They are more frequent in males.
  - Warmer temps, and lower steady state-Hb enhance ulcer formation.
  - Reoccurrence is common.

Symptoms

- Brain:
  - Strokes can occur when the brain cells don't receive adequate oxygen.
  - This affects 6-12% of patients.
- Anemia:
  - It occurs because there are too few RBC's, or too little hemoglobin in them.

Symptoms

- Kidney:
  - Sickling occurs more rapidly in the kidney than in any other organ.
  - This can lead to renal failure.
- Ears:
  - Hearing loss can also occur.

Diagnosis

- The diagnostic procedure can be performed as early as the 10^{th} week of development.
- It is performed on DNA from fetal cells obtained by amniocentesis (16^{th} week), or chorionic villus (10^{th} week) sampling.
- It is detected by gene mapping techniques, and is based on the sickle mutation altering the site at which the restriction enzyme Mst II cleaves the normal beta-globin gene.

Treatment

- Pain:
  - For mild to intermediate pain, acetaminophen or codeine is used.
  - For intense pain, morphine and intravenous fluids are given.
- Bone marrow transplantation:
  - It is dangerous, so it is not performed often.

Treatment

- Blood transfusions:
  - They are used for the prevention of certain complications of sickle cell disease.
  - Doctors have to make sure that they avoid excess blood viscosity.
  - Patients that were transfused before blood was screened (1975-85) had a risk of contracting AIDS.

Treatment

- Hydroxyurea:
  - It stimulates fetal hemoglobin (HbF), which has a higher affinity for oxygen, and as a result less aggregates will form.
  - It also increases the amount of Hb by suppressing bone marrow activity. When active bone marrow cells are suppressed the cells that make HbF go into red cell production.

New Developments (Treatments)

- Nitric Oxide:
  - It dilates blood vessels in the lungs.
  - This helps people with trouble breathing.
    - This benefits patients with acute chest syndrome by opening blood vessels in the lungs, and allowing blood cells to move through and pick up more O_2.

New Developments (Treatments)

- The first treatment of inhaled NO was approved by the FDA in Dec. 1999.
- It is thought that NO might also limit the sickling of blood cells by preventing the cells from sticking to blood vessel walls, or by diluting peripheral blood vessels.

New Developments (Treatments)

- It possibly works by:
  - Reducing the number of platelets and decreasing the number of blockages that deprive the tissue of oxygen.
  - Making blood cells less likely to adhere to blood vessel walls.
  - Binding directly to Hb, and preventing the formation of aggregates.
- It is a very safe treatment.

New Developments (Treatments)

- Sodium cromoglicate:
  - In a study, patients were given a single dose of sodium cromoglicate by inhalation or nasal route.
  - The percentage of sickle cells significantly decreased after treatment.
  - The effects were still detected 24 hours after treatment.
  - The antisickling mechanism is still unclear.
  - It costs very little, and has a very low toxicity.

New Developments (Treatments)

- Monoclonal antibodies:
  - Sickle cells are also thought to adhere to the vascular endothelium.
  - Two monoclonal antibodies, 7E3 and LM609 were shown to prevent red cell adhesion to the endothelium in rats.
  - They work by blocking ligand binding to integrin, a molecule which binds to several adhesion proteins.

New Developments (Treatments)

- Gene therapy:
  - Involving the transfer of the normal adult B-globin gene.
    - It is a major challenge. In addition to the universal difficulties of gene therapy, gene therapy of sickle cell disease also requires neutralization of the harmful effects generated by sickle Hb.

New Developments (Treatments)

- Involving postnatal overproduction of HbF.
  - It is a more promising therapeutic strategy for sickle cell disease.

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