Sickle Cell Disease: Genetics, signs and symptoms, Treatment

Sickle Cell Disease (SCD) refers to a group of inherited hemoglobinopathies characterized by the presence of **hemoglobin S (HbS)**, which polymerizes under low oxygen tension, causing red blood cells (RBCs) to assume a **sickle shape**. This was first reported in 1910 by **James Herrick**.

Genetics and Inheritance

- **Causative mutation**: A **single nucleotide substitution** (GAG ? GTG) in the **HBB gene** (?-globin gene) located on **chromosome 11**.
- **Amino acid change**: **Glutamic acid** ? **Valine** at the 6th position of the ?-globin chain.
- **Inheritance**: **Autosomal codominant**.
    - **Homozygous (SS)** ? Sickle Cell Anemia (severe disease).
    - **Heterozygous (AS)** ? Sickle Cell Trait (usually asymptomatic).
    - **Compound heterozygous states**:
        - **HbS/?-thalassemia**
        - **HbSC disease** (one ?-globin gene carries the S mutation, the other the C mutation).

Structure and Types of Hemoglobin

- **Hemoglobin A (HbA)**: 2 ? + 2 ? chains.
- **HbS**: 2 ? + 2 ?_S chains.
- **HbF (fetal hemoglobin)**: 2 ? + 2 ? chains (protective against sickling).
- **HbC**: Glutamic acid is replaced by **lysine** at position 6.

Pathophysiology

1. **Polymerization of HbS** occurs in **hypoxic, acidic**, and **dehydrated** environments ? sickling of RBCs.
2. Sickled RBCs:

- Are rigid and adhere to endothelium ? **vaso-occlusion**.
- Undergo hemolysis ? release **free hemoglobin**, depleting **nitric oxide** ? **vasoconstriction and endothelial dysfunction**.
- Induce **inflammation** via adenosine pathways.

1. **Vaso-occlusion + Hemolysis** = Tissue ischemia, organ dysfunction, chronic anemia.

Triggers of Sickling

- **Hypoxia**, **acidosis**, **dehydration**
- **Infections**, **cold exposure**, **stress**
- Presence of **HbC** (promotes sickling); **HbF** (protective)

Clinical Manifestations

Onset:

- Usually **after 6 months** of age when **HbF declines**.

1. Anemia-related symptoms:

- Pallor, fatigue, jaundice, gallstones

2. Vaso-occlusive events:

- **Pain crises** ("sickle cell crisis"): bones, chest, abdomen
- **Dactylitis (Hand-Foot Syndrome)** in infants
- **Acute chest syndrome**: cough, chest pain, fever, hypoxia
- **Stroke** (especially in children)

3. Organ damage:

- **Spleen**: functional asplenia ? recurrent infections
- **Liver**: hepatomegaly, biliary stones
- **Kidney**: hematuria, hyposthenuria, papillary necrosis
- **Heart**: cardiomegaly, murmurs, high-output failure
- **Eyes**: proliferative retinopathy
- **Bones**: avascular necrosis (femoral head), osteomyelitis
- **Skin**: chronic leg ulcers
- **Priapism**

Types of Crises

Crisis Type	Description
Vaso-occlusive	Most common; triggered by stress, dehydration; severe pain
Aplastic	Often due to **parvovirus B19**; reticulocytopenia
Splenic Sequestration	Sudden pooling of blood in spleen; hypovolemic shock (usually in children <2 years)
Hemolytic	Sudden increase in hemolysis; may occur with G6PD deficiency
Megaloblastic	Folate deficiency due to increased erythropoiesis

Diagnostic Evaluation

1. **CBC**:
    - Chronic anemia (Hb 6–10 g/dL), ? Reticulocytes
    - Leukocytosis, thrombocytosis
2. **Peripheral Smear**:
    - Sickled cells, target cells, Howell-Jolly bodies, nucleated RBCs
3. **Hemoglobin Electrophoresis**:
    - Confirms diagnosis
    - HbS >90% in homozygotes; no HbA
    - Variable HbF levels
4. **Bilirubin**:
    - Elevated **indirect bilirubin**
5. **Sickling Test**: Qualitative test with sodium metabisulfite
6. **Chest X-ray**: Acute chest syndrome
7. **Transcranial Doppler**: Screening for stroke risk in children

Management

Acute Management

- **Hydration**, **oxygen**, **analgesia** (opioids, NSAIDs)
- **Treat infections** aggressively
- **Blood transfusions** (esp. for severe anemia or stroke)
- **Hydroxyurea**: Increases HbF, decreases crises (first-line in severe disease)

Chronic Management

- **Folic acid supplementation**
- **Prophylactic Penicillin V** (from age 2 months to 5 years)
- **Vaccinations**:
    - **Pneumococcal** (PCV13 + PPSV23)
    - **Meningococcal**, **Hib**, **Hepatitis B**, **Influenza**
- **Regular monitoring**: CBC, liver/renal function, TCD scans (children)
- **Psychosocial support**
- **Bone marrow transplantation**: Potentially curative in children with matched donor
- **Gene therapy**: Promising future approach

Complications by System

System	Complication
CVS	Myocardial infarction, cardiomyopathy
Respiratory	Acute chest syndrome, pulmonary hypertension
CNS	Stroke, TIA, hemorrhage
Hepatobiliary	Gallstones, hepatic crisis
Renal	Hematuria, nephropathy, renal failure

System	Complication
Ocular	Retinopathy, blindness
Musculoskeletal	AVN, osteomyelitis
Reproductive	IUGR, infertility, miscarriage

Prenatal & Genetic Considerations

- **Prenatal diagnosis** via chorionic villus sampling (CVS) or amniocentesis
- **Genetic counseling** essential for carriers (HbAS)