SICKLE CELL ANEMIA

- Most common familial hemolytic anemia worldwide
- Common in Africa, Middle East, Saudi Arabia, African Americans
- Resistant to malaria falciparum infection
- Autosomal recessive
- Caused by single amino acid substitution (glutamic acid → valine) in β-chain
- In sickle cell disease (homozygous), Hg electrophoresis shows HgS and absent HgA
- In sickle cell carrier (heterozygous), Hg electrophoresis shows both HgA and HgS bands

PATHOGENESIS

- In deoxygentated case, HgS tends to polymerize in a longitudinal pattern, distorting cell shape and creating sickle shape
- The change is reversible by re-oxygenation, however, with repeated sicklings, cell membrane is damaged and hemolysis occurs
- The presence of normal HgA (carrier) and increased HgF (newborn) inhibits HgS polymerization
- Increased HgS concentration inside RBC promotes sickling (dehydration, acidosis), while the presence of additional α-thal decreases sickling

PATHOGENESIS

- Sickle-shaped RBCs take a longer time to pass through capillaries
- Removed by macrophages in spleen (extravascular hemolysis)
- Also adhere to endothelial cells, may create a thrombus

CLINICAL SYMPTOMS OF SSA

- Chronic moderate-severe hemolytic anemia, manifesting after the age of 6-months (dependent on fraction of sickled cells). The chronic course is interrupted by repeated sudden attacks of worsening anemia
- Vaso-occlusive crisis (independent on fraction of sickled cells), results in organ infarction. Commonly associated with systemic infection, inflammation, dehydration and acidosis.
- Hand-foot syndrome, acute chest syndrome, stroke, myocardial infarction, retinopathy, autosplenectomy
- Aplastic-crisis: infection by Parvovirus B19, causing worsening anemia, self-limited
- Susceptibility for encapsulated bacteria (pneumococcus, salmonella)
- Sickle cell carrier: asymptomatic

DIAGNOSIS

- Routine blood smear: presence of sickle cells, target cells
- Sickling test: adding hypoxic agent to RBCs promote sickling
- Hemoglobin electrophoresis
- DNA testing

G6PD DEFICIENCY

- Glucose 6-phosphate dehydrogenase deficiency
- X-linked inheritance
- Recurrent, transient episodes of intravascular hemolysis

TRIGGERS OF HEMOLYSIS

- Infection
- Certain drugs: sulfonamides, nitrofurantoin, large dose of aspirin, vitamin K, primaquine
- Fava beans
- In all, large amount of oxidants are generated, G6PD cannot neutralize them, causing hemoglobin denaturation and precipitate (Heinz bodies), damaging cell membrane and massive hemolysis of RBCs, 2-3 days after trigger
- Other cells lose demorfmability and partially phagocytosed inside spleen (bite cells)

CLINICAL SYMPTOMS

- Symptoms of intravascular hemolysis
- G6PD-A type: decreased amount of G6PD, bone marrow compensate by producing new RBCs
- G6PD-Mediterranian: qualitative defect of enzyme (low function), more severe symptoms
- Females: can have symptoms if random inactivation affects the normal X-chromosome

IMMUNE HEMOLYTIC ANEMIA (IHA)

- The presence of auto-antibody against RBC membrane protein
- These antibodies are detected by Coombs test
- Direct Coombs test: RBCs of patient are incubated with antibodies that target normal human antibodies (RBCs will agglutinate)
- Indirect Coombs test: patients serum is added to "test RBCs" that have certain surface proteins (identify the type of antigen)

WARM TYPE IHA

- High affinity auto-antibody (mostly IgG type)
- Binding occurs in core circulation (37°C)
- Removed by macrophages in spleen
- spherocytes develop, then destroyed by spleen (extravascular hemolysis)
- 60% are idiopathic, 25% associated with systemic lupus erythematosus, 15% by drugs (α-methyldopa, penicillin)
- Severity of anemia is variable, most patients have mild chronic anemia and splenomegaly

COLD TYPE IHA

- Low-affinity autoantibody (IgM)
- Binding occur in peripheral areas of body (<30°C)
- After IgM binding, few C3b molecules bind RBCs
- When RBCs return to core circulation, IgM dissociates, but C3b stays, identified by splenic macrophages and removed
- IgM binds 5 RBCs, thus creating in vivo agglutination, might block small capillaries in fingers and toes causing Raynaud phenomenon
- Transient forms of cold-IHA occur in recovery of infections by mycoplasma pneumonia and infectious mononucleosis (mild, self-limited)
- Chronic persistent form occur in B-cell lymphoma or idiopathic

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Rare, acquired disease
- Mutation in PIGA gene, results in deficiency in phosphatidylinositol glycan (PIG), a structural protein on cell membrane that anchors many other proteins
- Mutation occurs in bone marrow stem cell (leukocytes, RBCs and platelets are all affected)

PATHOGENESIS

- Complement system: circulating proteins that are part of immune system. They are activated (C5b-C9) and attack cell membrane to create pores, causing lysis
- Blood cells protect themselves by membrane proteins CD55 and CD59, that are normally attached to PIG
- RBCs, and to a lesser degree WBCs and platelets, are spontaneously lysed inside blood
- During sleep, ↑CO2, ↓ blood PH, more active complement system, more hemolysis
- Thrombosis is common

TRAUMATIC HEMOLYSIS

- Direct physical force, or turbulence causing lysis of RBCs
- Prosthetic heart valves
- Repetitive physical pounding (marathon, boxing, marching)
- Disseminated thrombi (microangiopathic hemolytic anemia)
- Hallmark of traumatic hemolysis: schistocytes

POLYCYTHEMIA

- Increase in total RBC mass
- Erythrocytosis: increased RBCs number
- Relative polycythemia: secondary to decreased plasma volume (water deprivation, severe diarrhea, diuretics)
- Absolute polycythemia: true increase in RBC mass, secondary to increased BM production (primary or secondary)
- Primary: polycythemia vera (low erythropoietin, splenomegaly)
- Secondary: adaptive (high altitude, cyanotic heart disease), paraneoplastc (renal cancer), surreptitious (endurance athletes). Erythropoietin in high, no splenomegaly