HEMOLYTIC ANEMIAS

INCREASE RED CELL DESTRUCTION =
REDUCED RED-CELL LIFE SPAN

HEMOLYTIC ANEMIAS

- A red blood cell survives 90 to 120 days in the circulation; about 1% of human red blood cells break down each day
- The spleen is the main organ which removes old and damaged RBCs from the circulation

MECHANISMS OF HEMOLYSIS

- Extravascular
  - ✓ red cells destruction occurs in reticuloendothelial system
- Intravascular
  - ✓ red cells destruction occurs in vascular space

SIGNS OF HEMOLYTIC ANEMIAS

- **Symptoms of anemia – pallor, fatique, rapid pulse**
- **Jaundice**
- **Splenomegaly**
- **(Fever, back pain, abdominal pain, rapid pulse)**

DIAGNOSIS OF HEMOLYTIC ANEMIAS

- **Anemia**
- **Reticulocytosis**
- **Indirect hyperbilirubinemia**
  - **Increased level of lactate dehydrogenase (LDH)**
  - **Absence or reduced of free serum haptoglobin**

INTRAVASCULAR HEMOLYSIS

- **Laboratory signs of intravascular hemolysis:**
  - tests for hemolysis

and aditionally:

- hemoglobinemia
- hemoglobinuria
- hemosiderynuria

HEMOLYTIC ANEMIAS

Compensated hemolysis – increase erythropoesis compensates increase destruction of erythrocytes

Decompensated hemolysis - erythropoesis can not compensate increae destruction – patient needs therapy

COMPLICATIONS OF INCREASED, CHRONIC HEMOLYSIS

- **Folinic acid deficiency**
- **Gallstones**
- **Thrombosis**
- **Hemolytic crisis - rapid destruction of large numbers of red blood cells**

Aplastic crisis - temporary failure of erythropoiesis

CLASSIFICATION OF HEMOLYTIC ANEMIAS

1. Hereditary
   a) Membrane defect (spherocytosis, elliptocytosis)
   b) Metabolic defect (Glucoze-6-Phosphate-Dehydrogenaze (G6PD) deficiency, Pyruvate kinase (PK) deficiency)
   c) Hemoglobinopathies (thalassemias, sickle cell anemia)

2. Acquired
   a) Immune hemolytic anemias
   b) Nonimmune hemolytic anemias

2. ACQUIRED

A. Immune hemolytic anemias

1. *Autoimmune hemolytic anemia*
   - caused by warm-reactive antibodies
   - caused by cold-reactive antibodies
2. Alloimmune hemolytic anemia (transfusion of incompatible blood)

B. Nonimmune hemolytic anemias

1. Chemicals
2. Bacterial infections, parasitic infections (malaria)
3. Hemolysis due to physical trauma
   (e.g. microangiopathic hemolytic anemia)
4. Hypersplenism
5. Paroxysmal nocturnal hemoglobinuria (PNH)

AUTOIMMUNE HEMOLYTIC ANEMIA - AIHA

- caused by warm-reactive antibodies (70%)
  - temp. 37°
  - usually IgG

- caused by cold-reactive antibodies (30%)
  – in temp. < 37 (4°)
  - usually IgM

AUTOIMMUNE HEMOLYTIC ANEMIA - AIHA

- warm-reactive antibodies

  - idiopathic

  - secondary: infections, connective tissue disorders, drugs

- cold-reactive antibodies

  – idiopathic

  - seconadary: infections (MP, Syphilis), CLL, NHL

AUTOIMMUNE HEMOLYTIC ANEMIA - AIHA

Laboratory findings:

- **test for hemolysis**
- **direct Coombs test (direct antiglobulin test)**

AIHA- TREATMENT

- Treatment of underlying disease
- Corticosteroids
  - Prednisone 1-2 mg/kg/day in divided doses
- Splenectomy
  - Failure to respond to prednisone
  - Dependence on prednisone dosages higher than 20 mg/day
  - Side-effects of the corticosteroids
- Immunoglobulins
- Immunosupressive agents
  - Cyclosporin, cyclophosphamide, azathioprine, 6-MP, MMF
- Rituximab therapy

- Avoid RBC transfusions

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ALLOIMMUNE HEMOLYTIC ANEMIA

- *Transfusion of incompatible blood*
- *Alloimune hemolytic disease of the newborn*
- *After transplantation of bone marrow or organs*

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      - caused by cold-reactive antibodies
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HEMOLYSIS DUE TO PHYSICAL TRAUMA

- Cardiac – most common
  - Prosthetic valve
  - Valvular disease e.g. stenosis

- Microangiopathic hemolytic anemia

MICROANGIOPATHIC HEMOLYTIC ANEMIA

- **Caused by many disease:**
- **DIC, disseminated malignancies, serious infection, complication of pregnancy, drugs**

MICROANGIOPATHIC HEMOLYTIC ANEMIA

- Intravascular hemolysis caused by fragmentation of normal red cells passing through abnormal arterioles
- Arterioles are changed by deposition of platelets and fibrin
- Microvascular lesion cause organ damage (kidney, CNS)

MICROANGIOPATHIC HEMOLYTIC ANAEMIA

- **Symptoms:**
  - **Related to the primary disease**
  - **Related to organs demage**
- **Laboratory findings – intravascular hemolysis**
- **Blood film: schistocytes**

MICROANGIOPATHIC HEMOLYTIC ANAEMIA

- Thrombotic thrombocytopenic purpura (TTP)
  - congenital – deficiency of ADAMTS13
  - acquired – autoantibodies against ADAMTS13

  ADAMTS13 cleaves von Willebrand factor multimers → microvascular platelet thrombosis → microvascular obstrucion and microangiopathic hemolytic anemia

- Hemolytic uremic syndrome (HUS)
  - Can occur after infection by E.coli, Shigella
  - Diarrhea – microangiopathic anaemia – renal failure

MICROANGIOPATHIC HEMOLYTIC ANAEMIA

Treatment

- Underlying disease, drug
- Plasma exchange – plasma infusion
- Glucocorticoids

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      - prosthetic heart valves
   4. *Hypersplenism*
   5. Paroxysmal nocturnal hemoglobinuria (PNH)

HYPERSPLENISM

- State of hyperactivity of the spleen

- Causes of hypersplenism
  - Splenic enlargement as a result of
    - blood stasis (Portal vein thrombosis, Congestive heart failure)
    - or cellular infiltration (MPN, NHL)
  - Infections (bacterial, viruses, fungi, tuberculosis)
  - Inflammatory diseases (Lupus erythematosus, Rheumatoid arthritis)
  - Storage disorders (Gaucher disease)
  - Other – amyloidosis, sarcoidosis

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- rare, progressive, life-threatening haematopoetic stem cell disorder
- characterized by chronic, complement-mediated intravascular hemolysis
- characterized also by prothrombotic state and chronic kidney disease

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Pathogenesis

- an acquired clonal disease, arising from a somatic mutation in a single abnormal stem cell
- deficiency of the GPI (glycosyl-phosphatidyl-inositol) anchor on the surface of hematopoietic cells
- red cells are more sensitive to the lytic effect of complement
- intravascular hemolysis

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Incidence – 1,3 / 1 mln persons / year

Estimated prevalence 15.9/ million

Symptoms

- Irregularly hemoglobinuria occurs with dark brown urine in the morning
- Hemolysis is released by infection, surgery or other events

- Increased risk of thrombosis

Paroxysmal nocturnal hemoglobinuria (PNH)

- LABORATORY FEATURES
  - **typical test for anaemia and hemolysis**

  - **HEMOGLOBINEMIA**
  - **HEMOGLOBINURIA**
  - **HEMOSIDERINURIA**

  - **CHRONIC URINARY IRON LOSS**
  - **SERUM IRON CONCENTRATION DECREASED**

  - **PANCYTOPENIA**

  - SPECIFIC IMMUNOPHENOTYPE OF ERYTROCYTES (CD59, CD55)
  - **POSITIVE HAM'S TEST (ACID HEMOLYSIS TEST)**

Paroxysmal nocturnal hemoglobinuria (PNH)

- **Not all patients need therapy**

Supportive treatment

- IRON AND FOLINIC ACID THERAPY

- **- ANTICOAGULATION**

- RBC TRANSFUSION

MONOCLONAL ANTIBODY ECULIZUMAB (SOLIRIS)

ALLOGENIC BONE MARROW TRANSPLANTATION

Corticosteroids ?

ECULIZUMAB (SOLIRIS)

- HUMANIZED MONOCLONAL ANTIBODY
- INHIBITS THE TERMINAL COMPLEMENT CASCADE BY BINDING TO HUMAN COMPLEMENT PROTEIN C5

- 600-900 mg infusion every week for 4 week,
- maintenance dose: 900 mg every 14 days

- PRICE: about 400 000 dollars/year

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- **Complications:**
  - **Thrombosis**
  - **Cytopenia**
  - **Progression to MDS or AML or AA**
  - **Renal failure**

- **Median survival ~ 10 - 15 lat**

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Hereditary membrane defects

1. Spherocytosis
   - **The most common defect of red cell membrane protein (1/2000 birth)**
   - **Inheritance - autosomal dominant**
   - **Deficient of membrane protein causes change of shape (round, no central pallor)**
   - **Clinical features: jaundice, gallstones, splenomegaly, constitutional skeleton changes (ie tower cranium, gothic palate)**
   - **Laboratory features: anemia, hiperbilirubinemia, retikulocytosis, ↑ LDH**
     - blood smear - microspherocytes
     - abnormal osmotic fragility test

SPHEROCYTOSIS - TREATMENT

- Folic acid supplementation
- Transfusions in pts with severe hemolysis
- Splenectomy in modarate/severe disease

Hereditary metabolic defect

- Glucoze-6-Phosphate-Dehydrogenaze (G6PD) deficiency
  - The most common human enzymopathy
  - Hemolysis is induce by infections, drugs, ingestion of the fava beans (favism)

G-6-PD DEFICIENCY- TREATMENT

- Avoiding of „oxidant” drugs
- Transfusions in severe cases
- Folic acid therapy

- Splenectomy can be considered

HEREDITARY HEMOGLOBINOPATHIES

- Thalassemias
  - Alfa thalassemia
  - Beta thalasemia: major, minor (trait), intermedia
  - Delta/Beta thalassemia
  - Hereditary persistentce of fetal hemoglobin
- Sickle cell anemia

SICKLE CELL ANEMIA

CHRONIC HEMOLYTIC ANEMIA CHARACTERIZED BY SICKLE-SHAPED RED CELLS

CAUSED BY HOMOZYGOUS INHERITANCE OF HEMOGLOBIN S

SICKLE CELL ANEMIA - INCIDENCE

- Occurs mainly in people of African, Caribbean, Mediterranean descent
- Homozygous - about 0,3% of Arficans Americans in the USA (have sickle cell anemia)
- Hetezygotes-8-13% of Africans Americans (are not anemic, but the sickling trait = sicklemia can be demonstrated in vitro)

SICKLE CELL ANEMIA -PATHOGENESIS

- **Hemolysis - because sickle RBCs are too fragile to withstand the mechanical trauma of circulation**

- **Occlusion in microvascular circulation caused by distorted, inflexible RBCs adhering to vascular endothelium**

SICKLE CELL ANEMIA - CLINICAL FEATURES

IN HOMOZYGOTES

- Onset in the first or second year of live
- Period episodes of acute vascular occlussion (painful crisis)
- Events which impair tissue oxygenation can precipitate crisis (f.e. pneumonia)
- Consequences of vaso-occlusion of the microcirculations (tissue ischemia and infarction) - infarction of spleen, brain, marrow, kidney, lung, aseptic necrosis, central nervous system and ophtalmic vascular lesions

SICKLE CELL ANEMIA-THERAPY

1. **Preventive measures:**

   prevention or remedy of: infections (penicillin prophylaxis and pneumococcal vaccination), fever, dehydratation, hypoxemia, acidosis, cold exposure

1. **Therapy of crises:**
   - **rehydratation, pain relief, antibiotic therapy,**
   - **blood transfusion in very severe cases**
2. **New approaches to therapy;**
   - **Activation of Hb F synthesis - 5-azacytidine**
   - **Antisickling agents acting on hemoglobin or membrane**
   - **Bone marrow transplantation**

THALASEMIAS

- Definition:
  - defects in the synthesis of one or more of the globin chains
- Etiology:
  - gene (located on chromosomes 11 and 16) deletion, rearangement of the loci, point mutations
- Epidemiology:
  - Thalasemias are the most common in the Mediterranean basin and near-equatorial regions of Asia and Africa
  - The regions in which thalasemia occured are contiguous with regions endemic for malaria (protection against malaria)

THALASEMIAS

- Consequences: underproduction of hemoglobin and accumulation of unpaired globin subunits
  - Reduced production of functioning hemoglobin tetramers (HbA: $\alpha_2\beta_2$)- hypochromia and microcytosis
  - Unbalanced accumulation of globin subunits- ineffective erytropoiesis and hemolytic anemia
    - 1. Precipitation of α globin chains (insoluble α tetramers)
    - 2. Formation of Hb H (β_4) incapable of releasing oxygen

DIFFERENT FORMS OF THALASSEMIAS

- **Beta-thalasemia: defect in beta-globin chain biosynthesis**
  - **major, intermedia, minor (trait)**
- **Alfa-thalassemia: defect in alfa-globin chain biosynthesis**
- **Delta/Beta thalassemia**
- **Hereditary persistence of fetal hemoglobin**

BETA-THALASSEMIA MAJOR (COOLEY'S ANEMIA; HOMOZYGOUS BETA-THALASEMIA)

- Diminished HbA synthesis- in the most severe variant no beta-chains are synthetized
- Clinical features:
  - Palllor, jaundice
  - Hepatosplenomegaly
  - Growth retardation
  - Facial and skeletal changes caused by bone marrow expansion
    - frontal bossing, expanded maxilla, widened diploe, gross skeletal deformities, spontaneous fractures, dental problem
  - Increased susceptibility to infection
  - Symptoms of iron overloading

BETA-THALASSEMIA MAJOR TREATMENT

- Transfusion – „hypertransfusion" programs
  - Hb should be maintained above 9 to 10,5 g/dL
  - Administration of 1 to 3 units of RBCs every 2 to 4 weeks
- Iron chelation therapy
  - Deferoxamine mesylate (Desferal, DFO) in daily 8-12 hrs sc infusion of 25-50/kg of DFO
- High standard of pediatric care required!
  - early treatment of infections
  - vaccination, folate supplementation, dental care
- Splenectomy
  - A progressive increase in transfusion requirements due to hypersplenism
- allogeneic HSCT
- Experimental therapy: hydroxyurea, somatic gene therapy