Anemias in children

Anemia…

… abnormal low hemoglobin, hematocrit or RBC count, lower than the age-adjusted reference range for healthy children.

Etiologic classification

I Impaired red cell formation

A/ Deficiency

- **Decreased dietary intake**
- **Increased demand**
- **Decreased absorption**
- **Increased loss**

B/ Bone marrow failure

- **Failure of a single or all cell lines**
- **Infiltration**

C/Dyshematopoietic anemia

II Blood loss

III Hemolytic anemia

- **Corpuscular (membrane, enzymatic or hemoglobine defects)**
- **Extracorpuscular (immune, idiopathic)**

Diagnosis of Anemia

- **detailed history**
- **careful physical examination**
- **peripheral blood smear**
  - **red cell morphology**
  - **MCV**
  - **RDW (red cell distribution width)**
  - **WBC and platelet morphology**

- **Additionally:**

-bone marrow evaluation

-additional testing

History

- **Diet (iron , folate, vitB12 intake, onset of hemolysis after certain foods –e.g.,fava beans)**
- **family history (transfusion requirements of relatives, splenectomy, gallblader disease)**
- **environmental exposures (lead poissoning)**
- **symptoms (headache, exertion dyspnea, fatigue, dizziness, weakness, mood or sleep disturbances, tinnitis)**
- **melena, hematemesis, abdominal pain- chronic blood loss**

Physical Examination

- **Pallor**
  (skin, oral mucosa, nail beds)
- **Jaundice -hemolysis**
- **tachycardia**
- **tachypnea**
- **orthostatic hypotension**
- **venous hum**
- **systolic ejection murmur**
- **peripheral edema?**
- **Splenomegaly?**
- **Hepatomegaly?**
- **Glossitis?**
- **gingival pigmentation?**
- **Adenopathy?**
- **Facial, extremity examination**

Peripheral Blood Components

important! Different values dependent on age!

- **RBC**
- **Hgb**
- **HCT**
- **MCV – 80 – 100 fl/L (a calculated value)**
- **MCH**
- **RDW**
- **Reticulocyte Count**

MCV for Characterize Anemia

Low(<70 fl)

***Hypochromic/Microcytic**

-Iron deficiency anemia

-Thalassemia

-Sideroblastic anemia

-Chronic infection

-Lead poisoning

-Inborn errors of Fe metabolism

-Severe malnutrition

-Copper deficiency

(>85fl)

***Macrocytic**

- **Normal newborn**
- **Increased erythropoesis**
- **Post splenectomy**
- **Liver disease**
- **Aplastic anemia**
- **Megaloblastic anemia**
- **Down S.**
- **Obstructive jaundice**

- **Normocytic**
  - **Acute blood loss**
  - **Infection**
  - **Renal failure**
  - **Connective tissue disorders**
  - **Liver disease**
  - **Disseminated malignancy**
  - **Early iron deficiency**
  - **Aplastic anemia**
  - **Bone marrow infiltration**
  - **Dyserythropoietic anemia**

Iron Deficiency Anemia

- **Causes**

-Dietary deficiency

-Increased demand (growth)

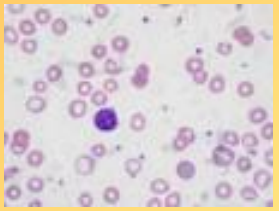
-Impaired absorption

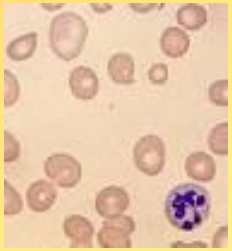
-Blood loss (menstrual problems)

- **Symptoms**

- **GI: Anorexia, poor weight gain, pica, atrophic glossitis**
- **CNS: fatigue, irritability**
- **Cardiac: increased cardiac output, cardiac hypertrophy**
- **Dry skin, thin hair, pallor, nail ridges**

Iron Deficiency Anemia





*characteristics of peripheral blood smear

- microcytic
- hypochromic

*MCV and Hgb– decreased (Hgb<12g/L)

- Ferritin – decreased (<13mg/dL)
- TIBC - high

-Serum iron –decreased (N 50-150 µg/dL)

Iron Deficiency Anemia

- **Treatment**
  - **oral iron supplementation: 4 - 6mg/kg/day of elemental iron**
  - **goal: to replace iron stores, not just circulating Hgb!**
  - **Reticulocytes- starts to rise in 3 -4 days,**
  - **Hbg- after 4- 5 days**
  - **After Hgb normalisation – continue Fe therapy 1-2 months to replace Fe stores**
  - ***Iron- rich foods:**
    animal protein, green vegetables, iron fortified cereales
  - **Folate, vit C**

parenteral therapy (IM,IV)

- **indications**
  - **poor compliance**
  - **severe bowel disease**
  - **intolerance of oral iron**
  - **chronic hemorrhage**
  - **acute diarrhea disorder**

Megaloblastic anemia

- **Presence the megaloblasts in the bone marrow and macrocytes in the blood**
- **In > 95% occurs as a result of folate and vitamin B12 deficiency**
- **Deficiencies of ascorbic acid, tocopherol, thiamine may be related to megaloblastic anemia**
- **Dietary vitamin B12 (cobalamine) is required from animal sources (meat and milk)**

Causes of vitamin B12 deficiency

I Inadequate dietary intake (<2mg/day) –malnutrition, veganism, maternal deficiency

II Defective vitamin B12 absorption

- **Failure to secrete intrinsic factor**
- **Failure to absorption in small intestine**

III Defective vitamin B12 transport

IV Disorders of vitamin B12 metabolism (congenital, acquired)

Folic acid deficiency

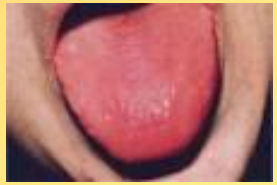
- **One of the most common micronutrient deficiences in the word (next to iron deficiency)**
- **Component of malnutrition and starvation**
- **Women are more frequently affected than men**
- **Folate sufficiency prevents neural tube defects**
- **Low mean daily folate intake is associated with twofold increased risk for preterm delivery and low infant birth weight**

Causes of folic acid deficiency

- **Inadequate intake (method of cooking, special diet, goat' milk)**
- **Defective absorption (congenital or acquired)**
- **Increased requirements (rapid growth, chronic hemolytic anemia, dyserythropoietic anemias, malignant disease, hypermetabolic state, cirrosis, post –BMT)**
- **Disorders in folic acid metabolism (congenital, acquired)**
- **Increased excretion**

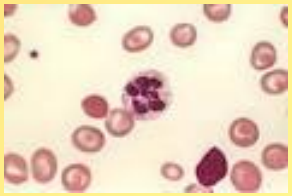
Clinical features of cobalamine and folate deficiency

- **Insidious onset: pallor, lethargy, fatigability, anorexia, sore red tongue and glossitis, diarrhea**
- **History: similarly affected sibling, maternal vitamin B12 deficiency or poor maternal diet**
- **Vitamin B12 deficiency: signs of neurodevelopmental delay, apathy, weakness, irrability, athetoid movements, hypotonia, peripheral neuropathy, spastic paresis**



Diagnosis

- **Red cell changes: Hgb usually reduced, *MCV increased to levels 110 – 140fl.*, MCHC normal,**
- **in blood smear many macrocytes and macro-ovalocytes, anisocytosis, poikilocytosis, presence of Cabot rings, Howell-Jolly bodies, punctate basophilia**
- **White blood cell count reduced to 1500 – 4000/mm^3, neutrophils show *hypersegmentation* (>5 lobes)**



- **Platelets count moderately reduced (50,000 – 180,000/mm^3)**
- **Bone marrow: megaloblastic appearance**
- **Serum vitamin B12 values lowered (normal 200 – 800 pg/ml)**
- **Serum and red cell folate levels – wide variation in normal range; less than 3 ng/ml -very low, 3-5 ng/ml –low, >5-6 ng/ml normal, in red cell:74-640 ng/ml**
- **Schilling urinary excretion test – measurement of intrinsic factor availability and absorption of vitamin B12**

Treatment

Vitamin B12 deficiency

Prevention in cases of risk of vitamin B12 deficiency

Treatment 25 – 100µg vitamin B12

Folic acid deficiency

- **Correction of the foliate deficiency (100-200µg/day)**
- **Treatment of the underlying causative disorder**
- **Improvement of the diet to increase folate intake**

Bone marrow failure

- **Isolated quantitative failure of one cell line, a single cytopenia , e.g. erythroid, myeloid, megakaryocytic**
- **A failure of all three cell lines (pancytopenia with hypoplastic or aplastic bone marrow)**
- **A quantitative failure of the bone marrow, e.g. congenital dyserythropoietic anemia**

- **The invasion of the bone marrow by non-neoplastic or neoplastic condition**

Diamond-Blackfan anemia
congenital pure red cell aplasia

The erythroid progenitor cell is intrinsically abnormal in the following aspects:

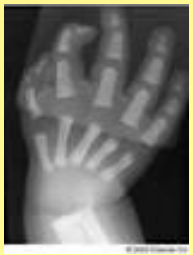
- **Decreased sensitivity to erythropoietin (EPO)**
- **Decreased sensitivity to EPO not corrected by IL-3 and GM-CSF**

***caused by*:**

- **Functional abnormalities in the erythropoietin receptors**
- **Erythroid progenitors are abnormally sensitive to a deprivation of erythropoietin, resulting in an accelerated rate of apoptosis**

Clinical features

- **Anemia and pallor in first 3 months, 35 % is anemic at birth, 65% -identified by 6 months of age and 90% - by 1 year**
- **Platelets and white cell count – normal**
- **25% have prenatal or postnatal growth failure and associated congenital defects, including short stature, abnormalities of thumbs, skeletal anormalities, congenital heart defects, webbed neck, urinary tract abnormalities and craniofacial dysmorphism**
- **Chromosomal studies generally normal**
- **No hepatosplenomegaly**
- **Malignant potential (increased incidence of ALL, AML, hepatocellular carcinoma)**



Diagnosis

- **Anemia and reticulocytopenia**
- **Bone marrow with virtual absence of normoblasts**

Differential diagnosis

- **Transient erythroblastopenia of childhood (TEC)**
- **Congenital hypoplastic anemia**

Treatment

- **Prednisone 2 mg/kg/day,**

  when the hemoglobin level reaches 10.0g/dl ⟶ dose reduction to minimum necessary
- **Packed red cell transfusion, leukocyte –depleted**
- **Bone marrow transplantation in steroid –resistant, transfusion-dependent patients**

Fanconi anemia

congenital aplastic anemia

- **Rare inherited disorder, autosomal-recessive trait**
- **Pancytopenia: develops between 4 and 12 years of age**
- **It may present with isolated anemia or leukopenia or anemia + thrombocytopenia**
- **Macrocytosis (high MCV), high HbF, high erythropoetin, presence of i antigen – characteristic of stress erythropoiesis**
- **Diepoxybutane (DEB)-induced chromosomal breakages**
- **Hypocellularity and fatty replacement in bone marrow**
- **congenital anomalies: patchy brown pigmentation of the skin, short stature, skeletal anomalies, hyperreflexia, hypogenitalism, microcephaly, microphthalmia, strabismus, ptosis, nystagmus, abnormalities of the ears, deafness, mental retardation, renal and cardiac anomalies**
- ***Chromosomal breakages and structural abnormalities, chromatoid exchange***
- **High incidence of AML, carcinoma**

Treatment:

Supportive:

- **Packed red blood cells and platelets (irradiated, leukocyte reduced)**
- **Chelation treatment in iron overload**
- **Androgen therapy**

Active:

- **Allogenic bone marrow transplantation**

Acquired aplastic anemia

pathophysiology

- **Immunologically mediated, tissue-specific, organ-destructive mechanism**
- **Exposition to an antigen ⟶ cells and cytokines of the immune system destroy stem cells in the marrow ⟶ pancytopenia**
- **Gamma –interferon plays a central role in the pathophysiology of AA**
- **T cells from AA patients secrete gamma-IFN and TNF – potent inhibitors of both early and late hematopoietic progenitor cells**
- **Cytotoxic T cells secrete also IL-2, which causes polyclonal expansion of the T cells**

Causes of acquired AA

Idiopathic (70%)

Secondary:

- **Drugs: cytostatics, antibiotics (sulfonamides, chloramphenicol), anticonvulsants (hydantoin), antirheumatics, antidiabetics, antimalarian**
- **Chemicals: insecticides**
- **Toxins: benzene, carbon tetrachloride, glue, toluene**
- **Irradiation**
- **Infections: viral (hepatitis A, B, C, HIV, EBV, CMV, parvovirus)**
- **Immunologic disorders: GvHD**
- **Preleukemia, MDS, thymoma**
- **Malnutrition**
- **Paroxysmal nocturnal hemoglobinuria**

Severity

- **Severe AA: bone marrow cellularity <25%**

  Granulocyte count <500/mm^3 platelet count <20,000/mm^3 reticulocyte count <40,000/mm^3
- **Very severe AA: granulocyte count <200/mm^3**

Clinical findings:

- **Anemia (pallor, easy fatigability, loss of appetite)**
- **Thrombocytopenia (petechiae, easy bruising, severe nosebleeds)**
- **Leukopenia (increased susceptibility to infections and oral ulcerations)**
- **Hyperplastic gingivitis**
- **No: hepatosplenomegaly and lymphadenopathy**

Laboratory findings

- **Anemia normocytic, normochromic**
- **Reticulocytopenia**
- **Leukopenia: granulocytopenia often < 1500/mm^3**
- **Thrombocytopenia: often < 30,000/mm^3**
- **Bone marrow: marked depression or absence hematopoietic cells and replacement by fatty tissue**
- **Normal chromosomal analysis**

Treatment

Severe AA:

- **Allogeneic BMT**
- **In the absence of availability of an HLA-matched sibling marrow donor - immunoablation (ATG, cyclosporine, methylprednisolone, growth factors- G-CSF)**

Hemolytic anemia

Corpuscular defects

→Membrane defects

→Enzyme defects

→Hemoglobin defects

→Congenital dyserythropoietic anemias

Extracorpuscular defects

→Immune

→Nonimmune

Clinical features
suggesting a hemolytic process

- **Ethnic factors: incidence of sickle gene factor in the black population (8%), high incidence of thalassemia in people of Mediterranean ancestry, high incidence of glucose-6-phosphate dehydrogenase deficiency among Sephardic Jews**
- **Age factors: anemia and jaundice in an Rh+ infant born to a mother Rh- or a group A or group B infant born to a group 0 mother**
- **History of anemia, jaundice, or gallstones in family**
- **Persistent or recurrent anemia associated with reticulocytosis**
- **Anemia unresponsive to hematinics**
- **Intermittent bouts or persistent indirect hyperbilirubinemia**
- **Splenomegaly**
- **Hemoglobinuria**
- **Presence of multiple gallstones**

Corpuscular hemolytic anemias

Membrane defects

- **Morphologic abnormalities: hereditary spherocytosis, elliptocytosis, stomatocytosis, acanthocytosis**
- ***Spectrin*** **is responsible for maintaining red cell shape, regulates the lateral mobility of integral membrane proteins and provides structural support for the lipid bilayer**

Hereditary spherocytosis

Genetics

- **Autosomal-dominant inheritance (75%), non-family history –25%**
- **Most common in people of northern European heritage**
- **Incidence of 1 in 5000**

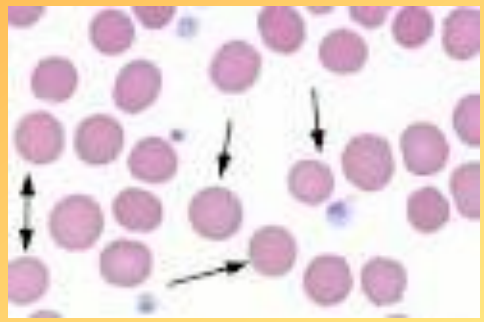
Pathogenesis

- **Membrane instability due to dysfunction or deficiency of a red cell skeletal protein: ankyrin (75-90%) and/or spectrin (50%)**

The sequelae are as follow:

- **Sequestration of red cells in the spleen (due to erythrocyte deformability)**
- **Depletion of membrane lipid**
- **Decrease of membrane surface area relative to volume, resulting in a decrease in surface area-to-volume ratio**
- **Tendency to spherocytosis**
- **Influx and efflux of sodium increased; cell dehydratation**
- **Increased glycolysis**
- **Premature red cell destruction**

Hematology



- **Anemia mild to moderate;**
  in erythroblastopenic crisis Hb may drop to 2 – 3g/dl
- **MCV usually decreased, MCHC raised**
- **Reticulocytosis**
- **Blood film – microspherocytes, hyperdense cells , polychromasia**
- **Coomb's test negative**
- **Increased red cell osmotic fragility – spherocytes lyse in higher concentrations of saline than normal red cells, occasionally only demonstrated after incubation of blood sample at 37 C for 24 hours**
- **Autohemolysis at 24 and 48 hours increased, corrected by the addition of glucose**
- **Reduced red cell survival**
- **Marrow- normoblastic hyperplasia, increased iron**
- **EMA-test**

Biochemistry

- **Raised bilirubin, mainly indirect reacting**
- **Obstructive jaundice with increased direct-reacting bilirubin; may develop due to gallstones, a consequence of increased pigment excretion**

Clinical features

- **Anemia and jaundice- severity depends on rate of hemolysis, degree of compensation of anemia by reticulocytosis, and ability of liver to conjugate and excrete indirect hyperbilirubinemia**
- **Splenomegaly**
- **Presents in newborn (50% of cases) with hyperbilirubinemia, reticulocytosis, normoblastosis, spherocytosis, negative Coomb's test, and splenomegaly**
- **Presence before puberty in most patients**
- **Sometimes diagnosis made much later in life by chance**

Complications

- **Hemolytic crisis – with pronounced jaundice due to accelerated hemolysis (may be precipitated by infection)**
- **Erythroblastopenic crisis – dramatic fall in Hb level and reticulocyte count, usually associated with parvovirus B19 infection**
- **Folate deficiency caused by increased red cell turnover, may lead to superimposed megaloblastic anemia**
- **Gallstones in 50% of untreated patients, incidence increases with age**
- **Rarely hemochromatosis**

Treatment

- **Folic acid supplement 1mg/day**
- **Leukocyte-depleted packed red cell transfusion for severe erythroblastopenic crisis**
- **Splenectomy for moderate to severe cases**

Hereditary elliptocytosis (HE)

- **Is due to various defects in the skeletal proteins, spectrin and protein 4.1 , it results increased membrane rigidity and in decreased cellular deformability**
- **Autosomal-dominant mode of inheritance**
- **Elliptocytes varies from 50 to 90%**
- **Osmotic fragility normal or increased**
- **Treatment: transfusion, splenectomy, prophylactic folic acid**

Another types of membrane defects

- **Hereditary stomatocytosis**
  (the cells contain high Na and low K concentrations)
- **Hereditary acanthocytosis**
- **Hereditary xerocytosis**

Enzyme defects

- ***Pyruvate Kinase deficiency*: defective red cell glycolysis**
- **Red cell rigid, deformed and metabolically and physically vulnerable**
- **Autosomal –recessive inheritance**
- **Nonspherocytic hemolytic anemia**
- **Variable severity: moderate severe anemia**
- **Neonatal jaundice**
- **Splenomegaly**
- **Gallstones, hemosiderosis, bone changes**

Treatment: folic acid supplementation, transfusions, splenectomy

Glucose-6-Phosphate Dehydrogenase deficiency

- **Sex-linked recessive mode of inheritance**
- **Disease fully expressed in hemizygous males and homozygous females**
- **Most frequent among blacks and those of Mediterranean origin**
- **Associations : hemolysis may be produced by drugs, fava (broad) bean, infections**

Clinical features

Drug induced hemolysis :

-Analgetics and antipyretics

-Antimalarian agents

-Sulfonamides

-Nitrofurans

-Sulfones

Favism:

-acute life-threating hemolysis often leading to acute renal failure caused by ingestion of fava beans

Associated with mediterranean and Canton varieties

Neonatal jaundice

Chronic nonspherocytic anemia

Treatment:

Avoid drugs deleterious in G6PD, splenectomy

Hemoglobin defects

→Thalassemias

- **Alpha chains hemoglobinopathies:**

  Deletion of two genes –alpha Thalassemia minor

- **Beta chain hemoglobinopathies (Hgb S, C,E, D)**

  Beta Thalassemia Major (impaired beta chain synthesis)

→Sickle Cell Disease : Hgb SS disease, Hgb S-C disease, Hgb S-beta

Sickle Cell Disease (SCD)

- **Most common abnormal hemoglobin found in US (8% of the black population)**
- **at birth the incidence is 1 in 625**

Genetics:

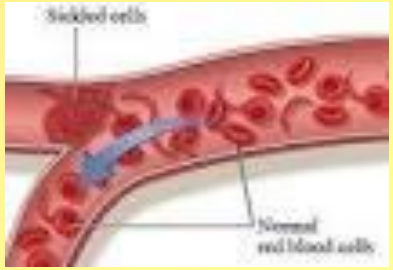
- **transmitted as an incomplete autosomal-dominant trait**
- **Homozygotes (two abnormal genes) do not synthetize Hb A, red cell contain 90-100% Hb S**
- **Heterozygotes (one abnormal gene) have red cell containing 20-40% Hb S**

Pathophysiology:

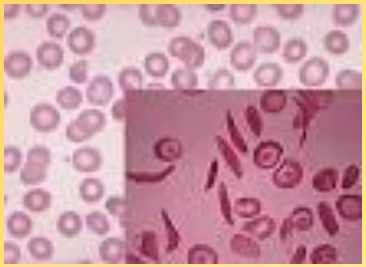
A single amino acid substitution: valine for glutaminic acid

(in the beta-polypeptide chain) ⟶

- **Different electrophoretic mobility**
- **HbS is less soluble than HbA**
- **Sickle cells are prematurely destroyed causing a hemolytic anemia**
- **Sickle cells result in increased blood viscosity and impaired blood flow and initiate thrombi**



Clinical features



- **Anemia- moderate to severe normochromic, normocytic**
- **Reticulocytosis**
- **Neutrophilia common**
- **Platelets often increased**
- **Blood smear: sickle cells, increased polychromasia, nucleated red cells, and target cells**
- **Erythrocyte sedimentation rate (ESR) – low**
- **Hemoglobin electrophoresis: HbS migrates slower than HbA, giving the diagnostic SS pattern**

Crises

- **Vaso-oclusive or symptomatic crisis:**
  - hand – foot syndrome (dactylitis) – hand-foot swelling
  - bone crises - osteonecrosis
  - CNS crises -thrombosis/ bleeding
  - pulmonary crises -dyspnea, severe hypoxemia
  - priapism - hematuria,
- **- intrahepatic vasoocclusive crisis**
- **Splenic sequestration crisis due to of pooling large amount of blood in the spleen) – splenomegaly, abdominal pain of sudden onset**
- **Erythroblastopenic crisis (cessation of red cell production)**
- **Hyperhemolytic crisis, unusual, in association with certain drugs or acute infections**

Organ dysfunction

- **Central nervous system (acute infarction of the brain) –motor disabilities, seizures, speech defects, deficit in IQ**
- **Cardiovascular system (cardiomegaly, myocardial dysfunction)**
- **Lungs (reduced PaO_2, reduced saturation, increased pulmonary shunting, acute chest syndrome)**
- **Kidneys (increased renal flow, increased GFR, enlargement of kidneys, hypostenuria, proteinuria, nephrotic syndrome)**
- **Liver and biliary system (hepatomegaly, cholelithiasis)**
- **Bones (dactylisis, avascular necrosis)**

- **Eyes (retinopathy, angioid streaks, hyphema – blood in anterior chamber))**
- **Ears (sensorineural hearing loss)**
- **Adenotonsillar hypertrophy**
- **Skin (cutaneous ulcers of the legs)**
- **Genitourinary (priapism)**
- **Growth and development (by 2 –6 years of age the height and weight delayed)**
- **Delayed sex maturation**
- **Functional hyposplenism (progressive fibrosis)**
- **Hemostatic changes (hypercoagulable state)**

Diagnosis

- **In utero: by PCR amplification of specific DNA sequences from fetal fibroblasts (obtained by amniocentesis)**
- **In newborn: electrophoresis for separation of hemoglobins**

Management

- **Comprehensive care (prevention of complications)**
- **Prophylaxis of infections pneumococcal vacccine, *H. Influenzae* vaccines, early diagnosis of infections**

Treatment modalities

Antisicking therapy :

- **fetal hemoglobin production stimulating agents (5-Azacytidine, hydroxyurea, recombinant EPO, short-chain organic acids)**
- **Red cell HbS concentration reducing agents (calcium channel blockers)**
- **Membrane active agents**
- **Hemoglobin solubility increasing agents**
- **Bone marrow transplantation**

Thalassemias

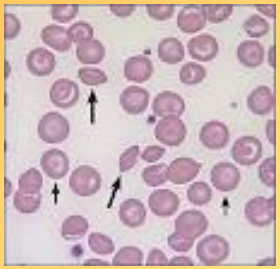
Beta-thalassemia – impaired beta-chain production

Alpha-thalassemia – impaired alpha-chain production

Genetic defects:

- **Two genes for Beta-globin synthesis (one on each chromosome 11) B-thalassemias are due to point mutations in one or both genes**
- **Four genes for a- globin synthesis (two on each chromosome 16) Most a-thalassemias are due to deletion of one or more a-genes**

Hematology



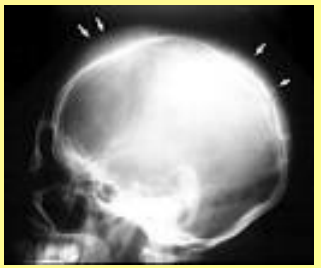
- **Hypochromic, microcytic anemia**
- **Reticulocytosis**
- **Leukopenia, thrombocytopenia**
- **Blood smear: target cells and nucleated cells, extreme anisocytosis, contracted red cells, polychromasia, punctate basophilia, circulating normoblasts**
- **HbF raised, HbA2 – increased**
- **Bone marrow: megaloblastic (due to folate depletion), erythroid hyperplasia**
- **Decreased osmotic fragility**
- **High serum ferritin**

Biochemisty

- **Raised bilirubin**
- **Evidence of liver dysfunction (late, as cirrhosis develops)**
- **Endocrine abnormalities (diabetes, hypogonadism)**

Clinical features

- **Failure to thrive in early childhood**
- **Anemia**
- **Jaundice, usually slight, gallstones**
- **Hepatosplenomegaly, hypersplenism**
- **Abnormal facies: prominence of malar eminence, frontal bossing, depression of bridge of the nose, exposure of upper central teeth**
- **Skull radiographs showing hair-on-end appearance due to widening of diploid spaces**
- **Fractures due to marrow expansion and abnormal bone structure**
- **Osteoporosis**
- **Growth retardation, primary amenorrhea, delayed puberty in males**
- **Leg ulcers**
- **Skin bronzing**
- **If untreated, 80% of patients die in the first decade of life**



Complications

Develop as a result of:

- **Chronic anemia**
- **Chronic transfusion → hemosiderosis and hemochromatosis**
- **Poor compliance with chelation therapy**

- **Endocrine disturbances: growth retardation, pituitary failure with impaired gonadotropins, IDDM, adrenal insufficiency, hypothyroidism**
- **Liver failure, cirrhosis**
- **cardiac failure due to iron myocardial iron overload**
- **Bony deformities due to extramedullary hematopoiesis**
- **Osteoporosis**

Management

- **Transfusion therapy (when Hb falls <7g/dl)**
- **hypertransfusion program used to maintain a pretransfusion Hb between 10.5 – 11.0 g/dl - corrects the anemia and suppresses ineffective erythropoiesis**
- **Chelation therapy to maintain serum ferritin close to 1000 ng/ml**
- **Splenectomy to reduce the transfusion requirements**
- **Bone marrow transplantation**
- **Gene therapy in future**
- **Increase HbF synthesis (trials): 5-Azacytidine, hydroxyurea, cytosine arabinoside, busulfan, butyric acid analogues**

Supportive therapy:

- **Folic acid**
- **Hepatitis B vaccination**
- **Treatment for congestive heart failure**
- **Endocrine invention**
- **Cholecystectomy**
- **Genetic counseling**
- **Management of osteoporosis (calcitonin, biphosphonates)**

Causes of death:

- **Congestive heart failure**
- **Arrythmia**
- **Sepsis secondary to increased susceptibility to infection post splenectomy**
- **Multiple organ failure due to hemochromatosis**

Extracorpuscular hemolytic anemias

- **Immune hemolytic anemia**
- **Warm autoimmune hemolytic anemia - responsible antibodies IgG class**
- **Cold autoimmune hemolytic anemia –IgM antibodies are cold agglutinins, and cold hemagglutinin disease,**
  cold hemagglutinin disease usually occurs during *Mycoplasma pneumoniae* infection
- **Nonimmune hemolytic anemia**
- **Microangiopathic hemolytic anemia caused by renal, cardiac, liver disease, infections.**