Disorders Of Hemoglobin (Hemoglobinopathy)

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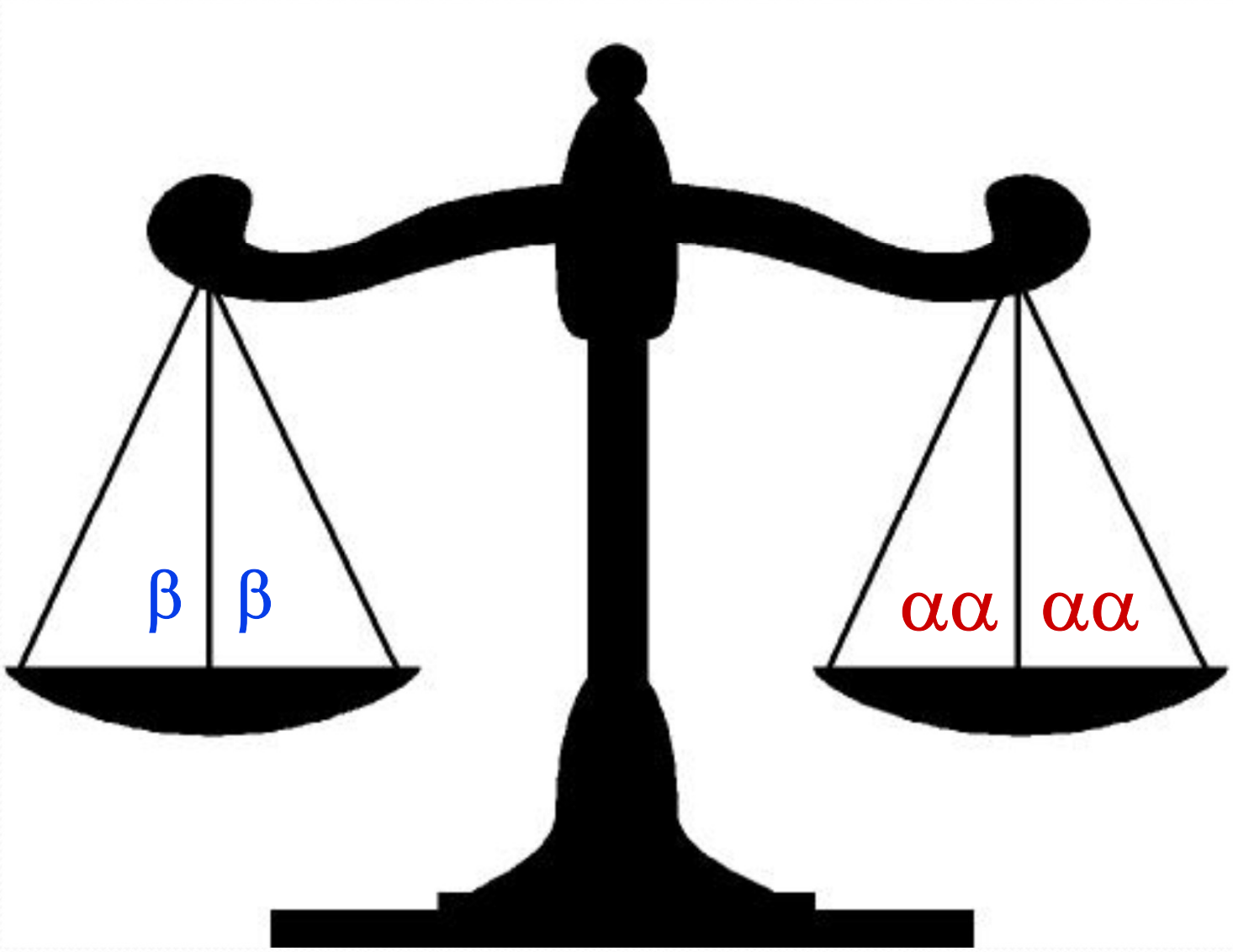
Classification

Quantative Hemoglobinopathy
Qualiative Hemoglobinopathy

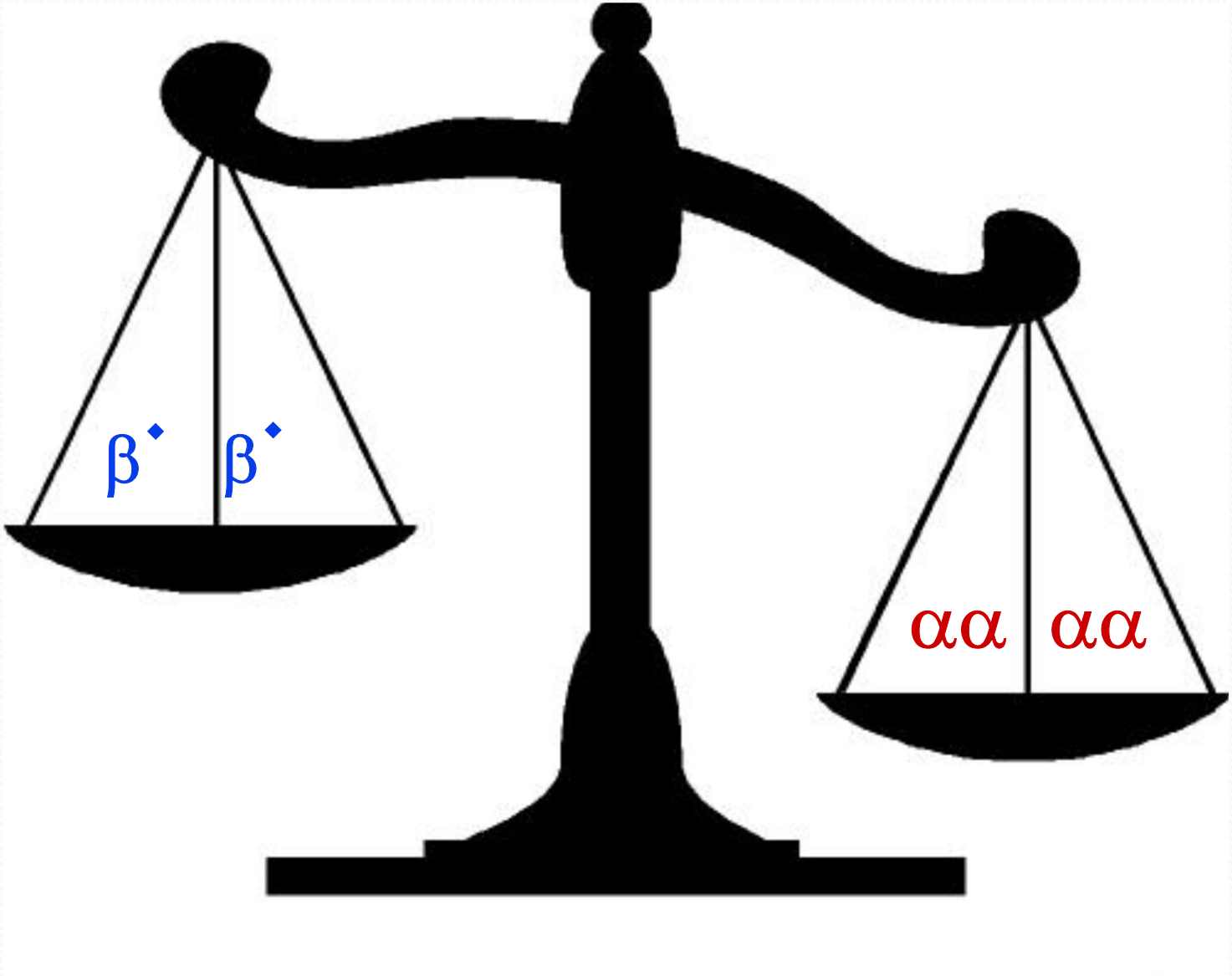
Quantative Hemoglobinopathy

Thalassemias syndromes are divided into α- and β-thalassemias, each with varying numbers of their respective globin genes mutated

Normal hemoglobin production: chain balance



Beta Thalassemia: chain imbalance



Genetic

There are four genes for α-globin synthesis (chromosome ١۶).

There are two genes for β-globin synthesis (chromosome ١١).

β -Thalassemia

Genetic

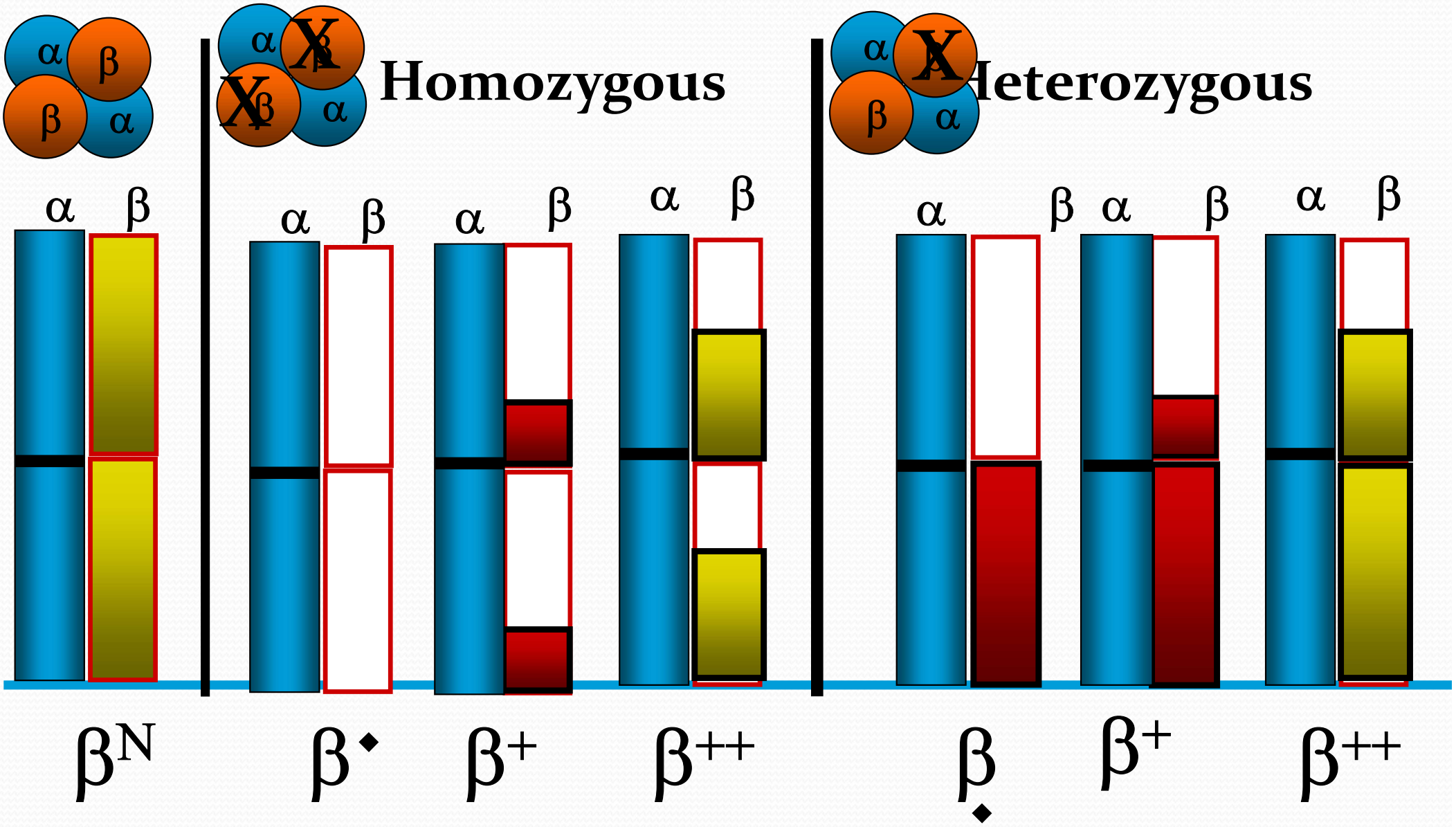
Most β-thalassemia due to point mutations in one or both of the two β-globin genes

Pathogenesis

Variable reduction of β-chain synthesis

Relative α-globin chain excess resulting in intracellular precipitation of insoluble α-chains.

Quantities of β globin chain produced in different genetic situations depends on the mutation type.



β-thalassemia Genotypes

$\beta\beta^{+}$

$\beta^{o}\beta$

$\beta^{+}\beta^{+}$

$\beta^{o}\beta^{+}$

$\beta^{o}\beta^{o}$

β-THALASSEMIA Silent&Trait

Silent Carrier

A silent carrier state for β -thalassemia was recognized through the study of families in which affected children had a more severe β -thalassemia syndrome than a parent with typical β -thalassemia trait

Silent Carrier

Characteristically, silent carriers of βthalassemia have normal levels of HbA_2

β -Thalassemia Trait

β - thalassemia are characteristically hypochromic and microcytic, in contrast to silent carriers, whose red cells appear near normal

β-Thalassemia Trait

Microcytosis, hypochromia,targeting, basophilic stippling, and elliptocytosis may be striking features, although the red cells may be nearly normal in occasional patients.

High-A٢ β -Thalassemia

Most common form of β thalassemia trait.

HbA٢ levels vary from ٣٫٥% to ٨٫٠%, whereas the HbFlevel varies from less than ١% to ٥%

High F β - *Thalassemia*

Individuals heterozygous for these mutations have increased levels of HbF (٥% to ١٥%) and low HbA٢ levels.

High-A٢ High-F β - Thalassemia

Level of HbA٢ is elevated and the level of HbF is also elevated (٥% to ٢٠%)

Clinical Features

Asymptomatic (physical exam is normal).

Discovered on routine blood test – slightly reduced hemoglobin, basophilicstippling, low MCV, normal RDW.

Discovered in family investigation or family history of heterozygous or homozygous β-thalassemia.

Clinical Features

Iron or folic acid deficiency, pregnancy, or intercurrent illness may exacerbate the anemia in patients with thalassemia trait.

β-THALASSEMIA INTERMEDIA

Clinical Features

Marked medullary expansion, which may result in nerve compression, extramedullary hematopoiesis, hepatosplenomegaly, growth retardation and facial anomalies may occur in untransfused patients

Clinical Features

Patients generally do not require transfusions and maintain a hemoglobin between ٧ and ١٠.

Transfusion

During periods of erythroblastopenia(aplastic crises) or during acute infection
Hb below ٧ g/dl

Failure to thrive

β-THALASSEMIA Magor

Clinical Features

Failure to thrive in early childhood

Anemia

Jaundice, usually slight

Hepatosplenomegaly
hypersplenism

Iron overload Complications

Due to repeated red cell transfusions in β-thalassemia major & increased absorption of dietary iron in β-thalassemia intermedia

Bone abnormalities

BM expansion with cortical thinning and bony abnormalities.
Abnormal facies, prominence of malar eminences, frontal bossing, depression of bridge of the nose.
Fractures due to marrow expansion.
Generalized skeletal osteoporosis.

Hepatic abnormalities

Hepatomegaly is due to progressive engorgement of hepatic parenchymal and phagocytic cells with hemosiderin deposits rather than extramedullary hematopoiesis.
Increased iron absorption and iron overload
Fibrosis/cirrhosis of the liver.

Cardiac abnormalities

Cardiac failure due to myocardial iron overload often associated with arrhythmias & pericarditis may occur .
Cardiac hemochromatosis causing arrhythmias and cardiac failure.

Cardiac abnormalities

Pulmonary hypertension occursin both β-thalassemia major and β-thalassemia intermedia.
Pulmonary hypertension and increased risk of thrombosis, particularly insplenectomized patients.

Endocrine abnormalities

Pituitary failure with hypogonadism, diabetes mellitus,hypothyroidism, hypoparathyroidism, adrenal insufficiency

Diabetes mellitus

Common and often under-recognized complication of thalassemia, is due to both pancreatic hypoproduction and (at least in some patients) insulin resistance

Thyroid

Even though iron deposition in thyroid parenchymal tissue is often extensive, dysfunction is usually limited to primary subclinical hypothyroidism.

Parathyroid

Symptomatic parathyroid disease manifested by classic tetany, hypocalcemia, and hyperphosphatemia is said to be an uncommon complication of iron overload.

Sexual hormon

Sexual maturation is variably observed in other patients and is retarded in patients whose transfusion and chelation therapy is inadequate. Failure of patients receiving transfusions to mature sexually may be the first indication of iron toxicity

Growth retardation

Impaired growth hormone production
Failure of adrenal androgen
Thyroid deficiency

Laboratory Findings

Anemia – hypochromic, microcytic

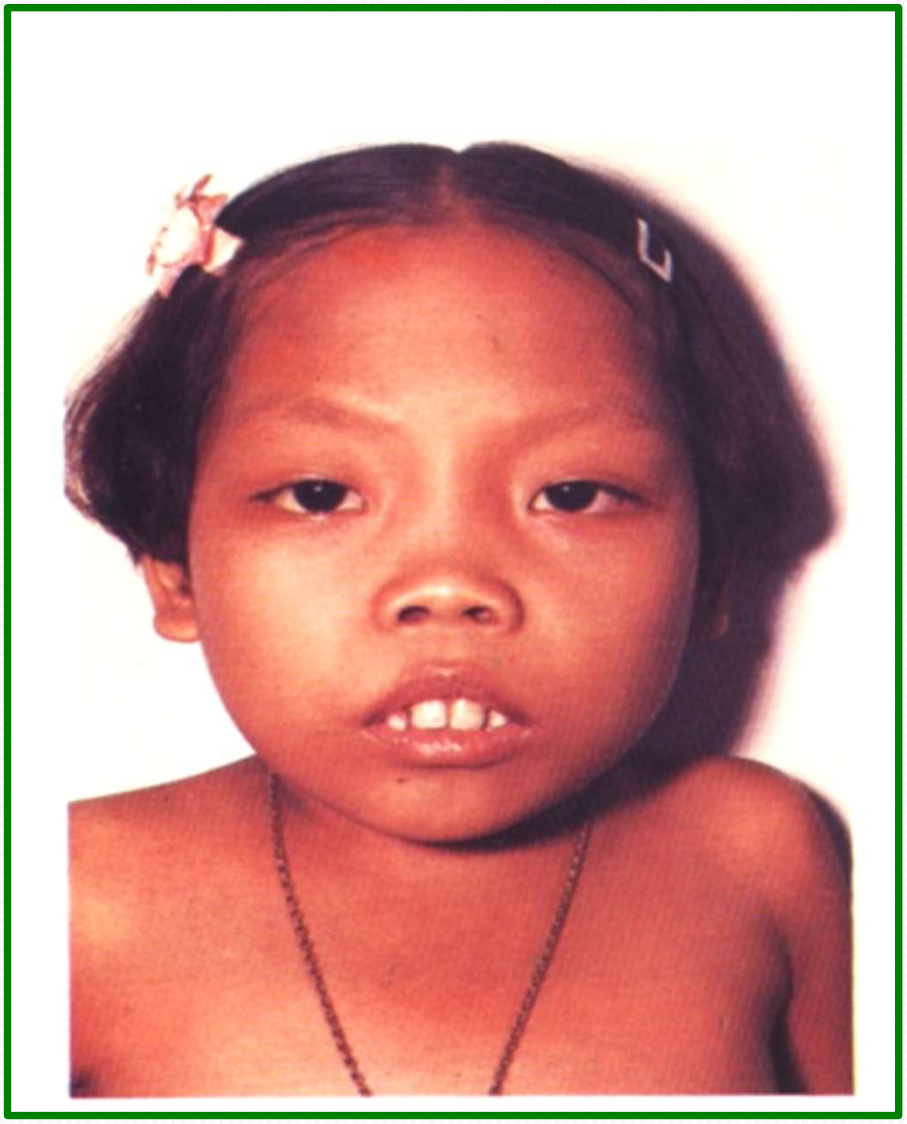
Reticulocytosis.

Leukopenia and thrombocytopenia

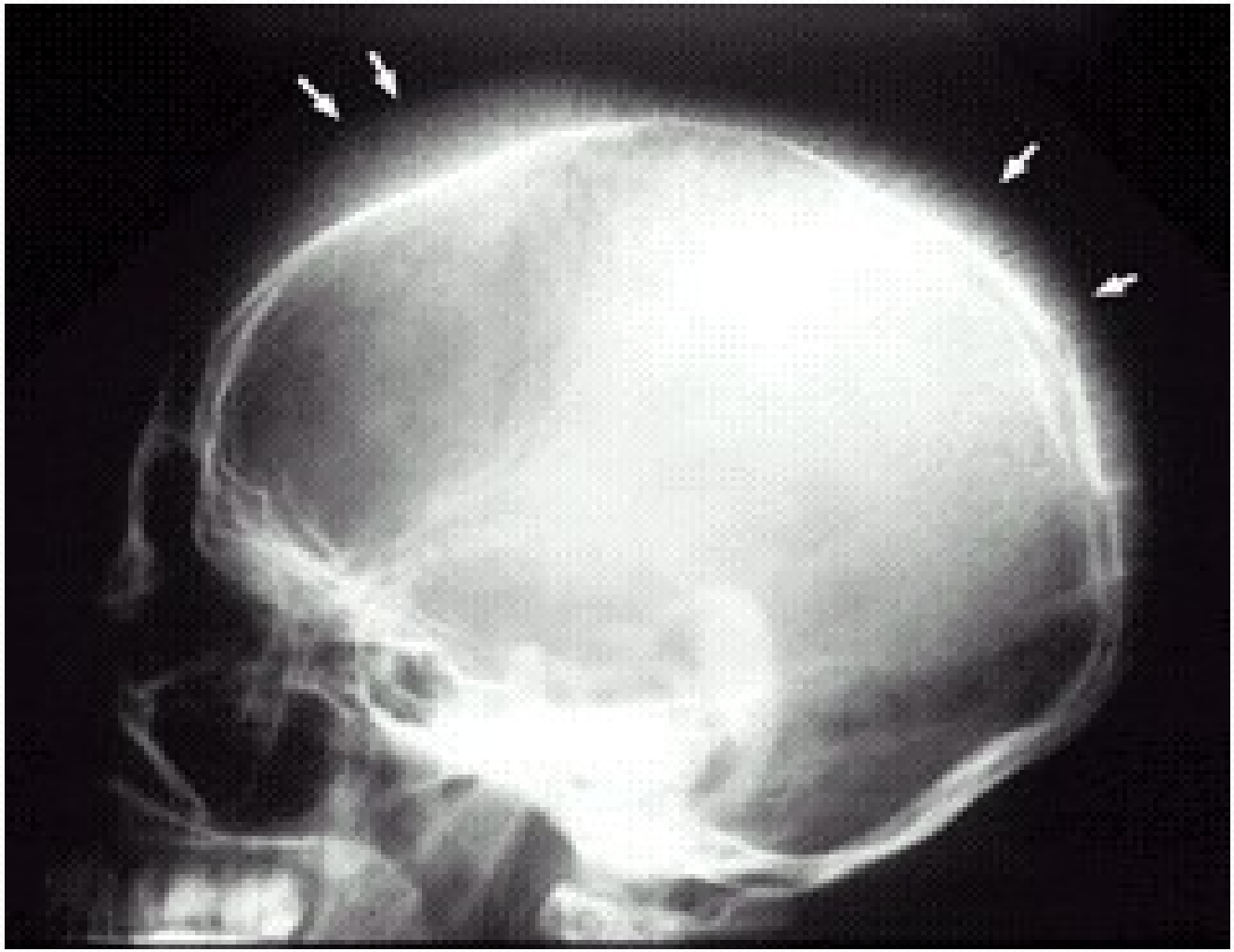
Blood smear – target cells and nucleated red cells, extreme anisocytosis, polychromasia

Hb F raised; HbA^{2} increased.

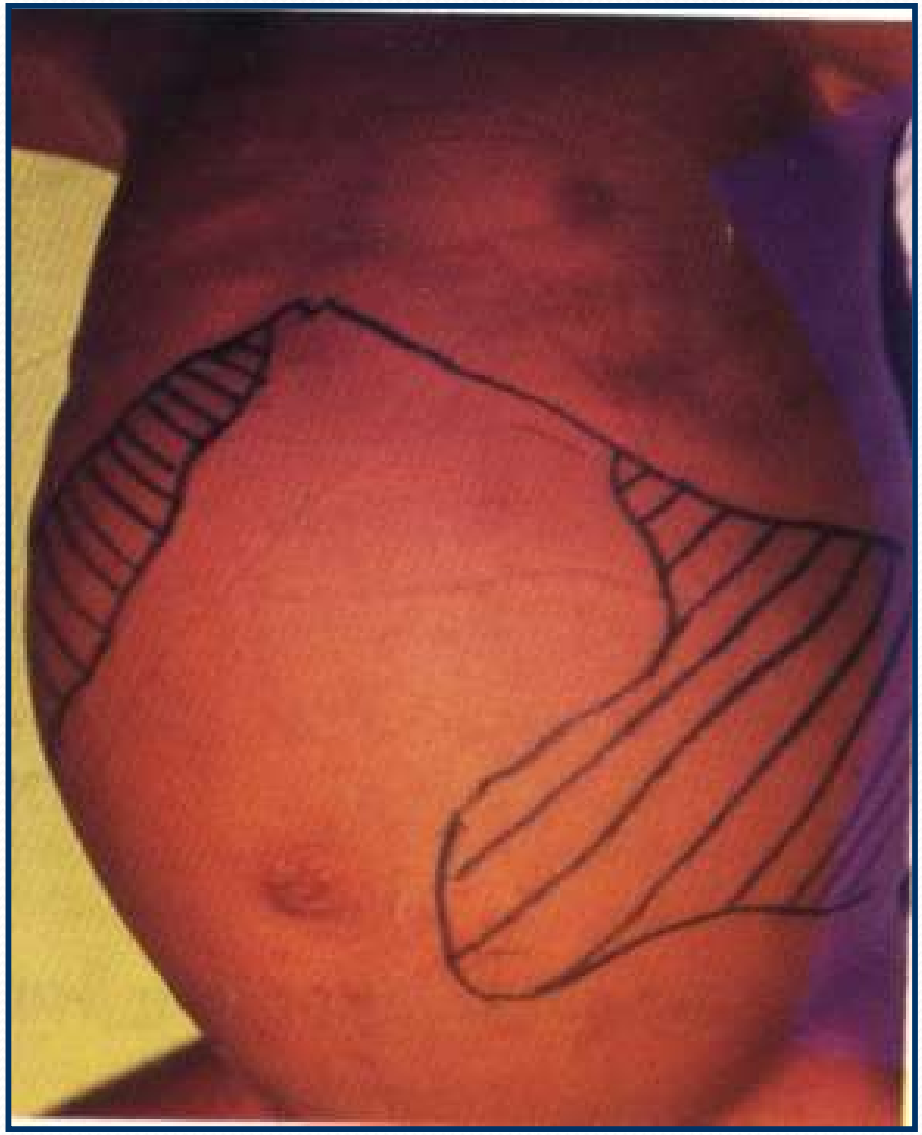
Thalassemia face



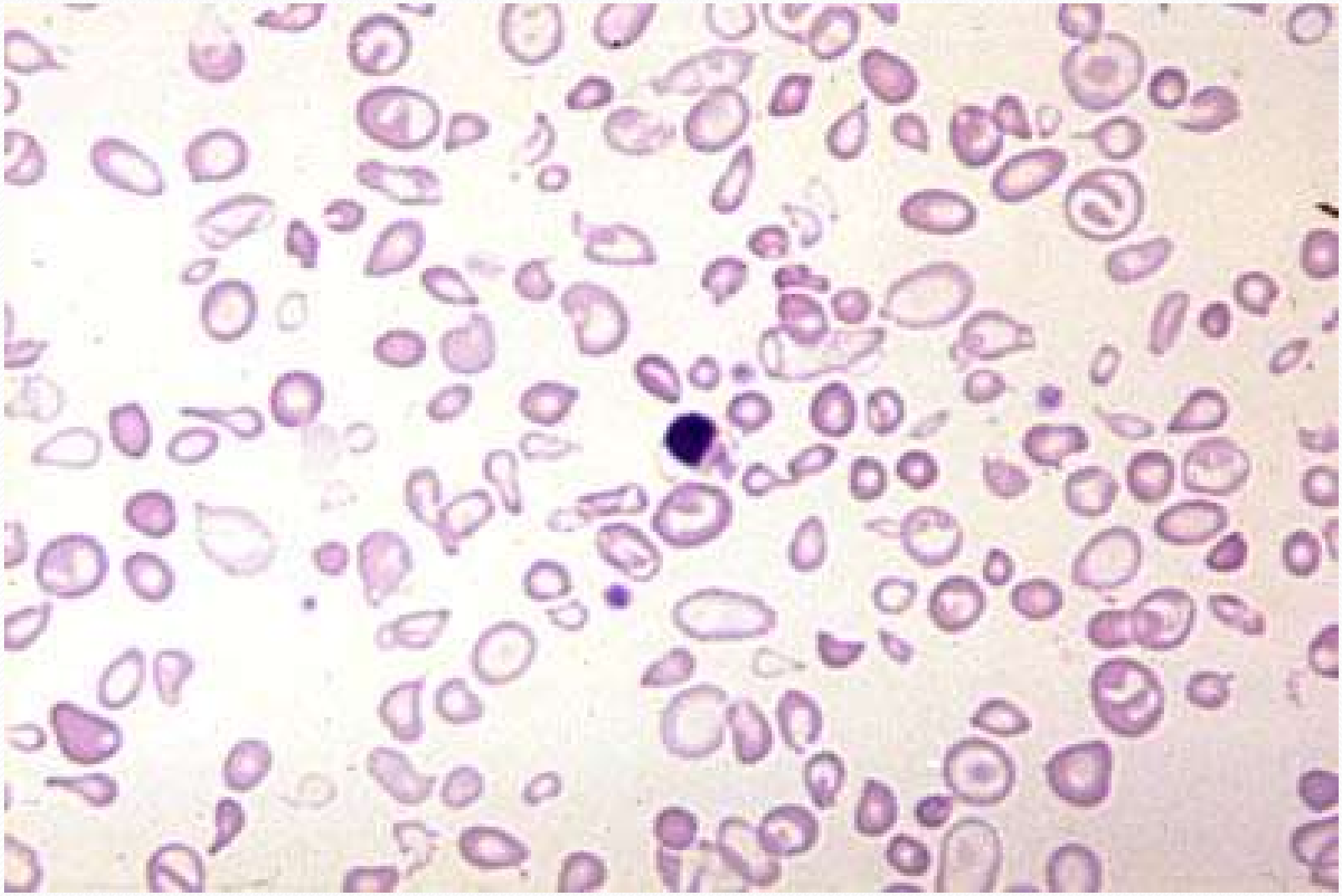
Hair on End Appearance



Hepatosplenomegaly



β Thalassemia Major



Anisopoikilocytosis, NRBC, microcytosis, hypochromia

Transfusion

Transfusion if initiated in the first year of life, promotes normal initial growth and development,limits the development of hepatosplenomegaly,prevents disfiguring bone abnormalities, reduces intestinal iron absorption, and decreases cardiac workload

Transfusion

If the hemoglobin level falls to less than ٧ transfusion program should be initiated to maintain the hemoglobin level at ٩٫٥ to ١١٫٥ .
First recommended a pre transfusion hemoglobin level of ٨٫٥ g/dL.

Transfusion

The goal of transfusions is to maintain a pretransfusion hemoglobin greater than ۹–۹٫۵ .

Post-transfusion hemoglobin falls roughly ۱ g per week, necessitating transfusions every ۳–۴ weeks.

Monitoring Iron Overload

Serum ferritin – particularly useful to follow trends
Value may be altered by infection,inflammation

Liver iron concentration (LIC)

Liver biopsy is the gold standard, but invasive. This is the method of choice if histopathological examination is needed

Liver iron concentration (LIC)

Liver iron concentration ١٥ mg/g dry weight of liver is associated with an increased risk of cardiac disease and death.

Cardiac iron concentration

Cardiac iron may be high even if the liver iron concentration is low, particularly in patients with a history of high iron levels in the past with recent intensification of chelation

Cardiac iron concentration

Cardiac iron measurment by T٢* MRI is most common are available

T٢* ٢٠ ms indicates minimal cardiac iron loading

T٢* ١٠–١٩ ms indicates some cardiac iron loading T٢* ١٠ ms is associated with a high risk of cardiac disease

α -Thalassemia

Genetic

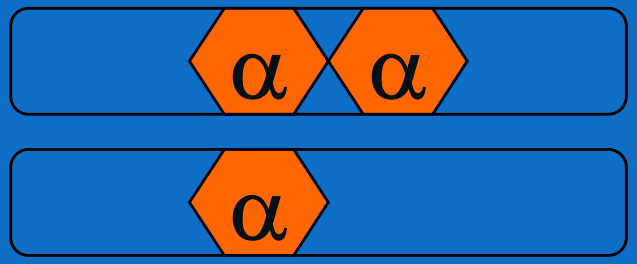
Most α-thalassemia syndromes are due to deletion of one or more of the α-globin genes rather than to point mutations.

α -Thalassemia

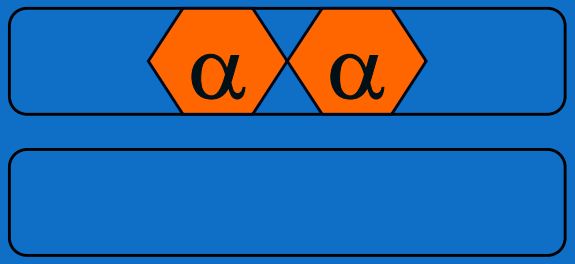
a-Thalassemia is divided into four clinical subsets that reflect the extent of impairment in a-globin chain production

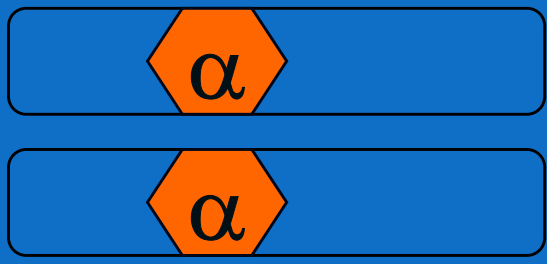
α - Thalassemia

Chromosome ١٦



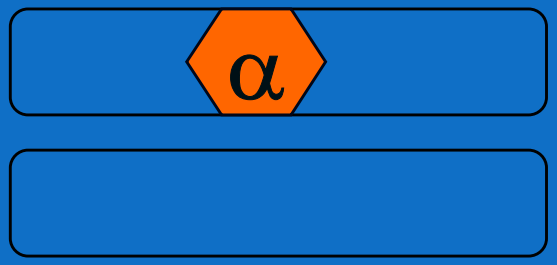
Silent carrier



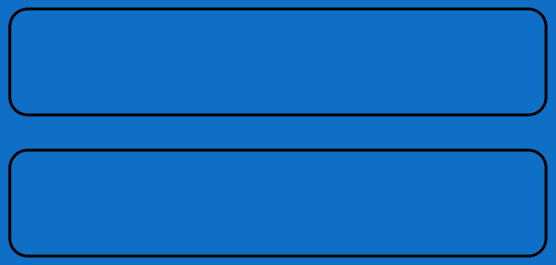


α - thalassemia trait
(+/- anemia)

HbH disease



(severe anemia)



Hydrops fetalis
(lethal in utero)

Hb Bart

α - Thalassemia

- Normal αα/αα
- Silent carrier - α/αα
- Minor -α/-α
  --/αα
- Hb H disease --/-α
- Barts hydrops fetalis --/--

Silent Carrier

The silent carrier state is due to the presence of a mutation affecting only one *a* globin gene. Most often this occurs because of a deletion mutation *(- α/αα)*

Silent Carrier

Mean MCV of patients with three functional genes is slightly lower than that in normal subjects.
The proportion of Hb Bart's may be levels of ١% to ٢% are attained in infants who are later shown to have silent carrier

α-Thalassemia Trait

Two genotypes ($-\alpha/-\alpha$ $--/\alpha\alpha$)

that reflect inactivation of two α-globin genes are associated with α-thalassemia trait.

Thalassemia Trait

The extent of the observed changes in red cell indices mirrors the reduction in *α*-globin production seen with each genotype, with the (-*α*/-*α*) genotype being less affected than the(--/*αα*)*genotype*.

α-Thalassemia Trait

Marked microcytosis and hypochromia of red cells in conjunction with mild anemia and erythrocytosis.

Levels of HbA_2 and HbF are generally normal or low.

α -Thalassemia Trait

Diagnosis of this condition is typically made by family studies or by exclusion of iron deficiency and β -thalassemia trait.

α-Thalassemia Trait

The proportion of Hb Bart's may be as high as ١% in the blood of normal newborns, but levels of ٤% to ٦% are attained in infants who are later shown to have α-thalassemia trait

Hemoglobin H Disease

HbH disease occurs in individuals who have only a single fully functional α -globin gene.
Anemia of moderate severity characterized by hypochromia,microcytosisand the presence of a fast migrating hemoglobin, HbH on electrophoresis

Hemoglobin H Disease

These excess chains form HbH, which accounts for ٥% to ٣٠% of the total hemoglobin in patients with HbH disease.
At birth,patients with HbH disease also have large amounts(٢٥%) of Hb Bart's (γ_4)

Hemoglobin H Disease

Typical patients with HbH disease live quite normally.

Anemia is moderate with a hemoglobin concentration of ٧ to ١٠ although occasional patients may have hemoglobin levels as low as ٣ to٤

Hemoglobin H Disease

The complications of HbH disease are related to chronic hemolysis.
Jaundice and hepatosplenomegaly are commonly present

Hemoglobin H Disease

Iron overload is uncommon but may occur in patients receiving transfusions and those older than ۴۵years

Hemoglobin H Disease

Hemoglobin H disease is clinically milder than homozygous β-thalassemia and usually does not require regular red cell transfusions.
Hemoglobin levels may fall with intercurrent illnesses and patients may require transfusion at such times

Hydrops Fetalis

Homozygosity for the *a* haplotype **(--/--)**

leads to hydropsfetalis.

Generally, affected infants are delivered stillborn at ٣٠ to ٤٠ weeks' gestation or die shortly after delivery

Hydrops Fetalis

Intrauterine transfusion of fetuses with hydrops fetalis should also be considered if treatment after delivery is contemplated.

Marrow transplantationmay be considered if the affected infant is delivered safely.

Hydrops Fetalis

Hydrops fetalis is not compatible with life and presents

with intrauterine or neonatal death, though some babies have survived with fetal packed redblood cell transfusions when antenatal diagnosis was made.

Qualative Hemoglobinopathy

Qualative Hemoglobinopathy

Sickle cell disease , Sickle cell trait, Sickle β-Thalassemia, Hemoglobin C,E,D

Incidence

Sickle hemoglobin is the most common abnormal hemoglobin found in the United States (approximately ٨% of the African-American population has sickle cell trait). The incidence of sickle cell disease (SCD) at birth is approximately ١ in ٦٠٠ African-Americans.

Genetics

Sickle cell disease is transmitted as an autosomal co-dominant trait.

Homozygotes (two abnormal genes, SS) do not synthesize hemoglobin A (Hb A) beyond infancy, red cells contain٧٥% hemoglobin S (Hb S).

Heterozygotes (one abnormal gene), sickle cell trait, have red cells containing ٢٠–٤٥% Hb S.

Pathophysiology

Hemoglobin S arises as a result of a point mutation (A–T) in the sixth codon of theβ-globin gene on chromosome ١١, which causes a single amino acid substitution (glutamic acid to valine at position ٦ of the β-globin chain).

Clinical Manifestations

Sickle Cell Crisis

Vaso-occlusive episodes are the major clinical manifestations of SCD and occur most commonly in the bones, lungs, liver, spleen, brain, and penis.

Sickle Cell Crisis

Painful crisis was the first symptom in more than a fourth of the patients and the most frequent symptom after the age of ٢ years.

Sickle Cell Crisis

The most common acute vaso-occlusive crisis is acute pain.
Virtually all patients with SS disease experience some degree of acute pain.

Sickle Cell Crisis

The underlying pathology is bone marrow ischemia,sometimes leading to frank infarction with acute inflammatory Infiltrates.
The most frequently involve are the lumbosacral spine, knee, shoulder, elbow,and femur.

Sickle Cell Crisis

Infections, physical stress ,dehydration, hypoxia, acidosis, changes in climate(cold), psychological factors may precipitate pain episodes,although commonly no precipitating factors can be identified.

Sickle Cell Crisis

painful dactylitis ("hand foot syndrome") is typically the first clinical manifestation of SCD.

Most common in children younger than ٣ years old.

Painful swelling of the dorsum of the hands and/or feet.

Sickle Cell Crisis

Often involves long bones, sternum, ribs, spine and pelvis.
May involve more than one site during a single episode.
Swelling and erythema may be present.

Sickle Cell Crisis

The differential diagnosis is very difficult because there is no definitive objective hallmark of a vasoocclusive.

Acute Chest Syndrome

Acute Chest Syndrome(ACS) is a leading cause of morbidity and mortality.

It represents the second most common acute complication(pain episode is first).

Acute Chest Syndrome

ACS is an acute illness with lung injury characterized by any combination of chest pain, fever, or respiratory symptoms and accompanied by a new pulmonary infiltrate on a CXR.

Acute Chest Syndrome

About ٥٠% of ACS events are associated with infections, including viruses, atypical bacteria including mycoplasma and chlamydia andless frequently with Streptococcus pneumoniae and Parvovirus B١٩.

Acute Chest Syndrome

The diagnostic criteria most commonly include radiographic evidence of a new segmental pulmonary infiltrate and one or more of the following:
fever, tachypnea, cough, newonset hypoxia, increased work of breathing (intercostal retractions, nasal flaring, accessory muscle use), or chest pain.

Acute CNS Event

Acute infarction of the brain can result in a devastating stroke, which occurs in approximately ٧% of children with SCD.

Acute CNS Event

Chronic injury to the endothelium of vessels by sickled red blood cells results in changes in the intima with proliferation of fibroblasts and smooth muscle; the lumen is narrowed or completely obliterated.

Acute CNS Event

Hemiparesis
Focal seizure
Gait dysfunction
Speech defects

Acute CNS Event

BrainCT- scan useful for detecting intracranial hemorrhage and often more readily available than MRI.

May not be positive for acute infarction within the first ۶ hours.

Brain MRI is more sensitive to early ischemic changes and may be abnormal within one hour.

Acute Abdominal Pain

The cause of this syndrome is unknown, although mesenteric sickling and vertebral disease with nerve root compression have been suggested.

Microvascular occlusion of mesenteric blood supply and infarction in the liver, spleen, or lymph nodes that results in capsular stretching.

Acute Abdominal Pain

This type of crisis can be accompanied by guarding, tenderness,rebound, fever, and leukocytosis that are indistinguishable from an acute surgical abdomen.
Symptoms of abdominal pain and distension mimic acute abdomen

Priapism

Priapism is defind as an unwanted painful of penis often occurs during the early morning, when normal erections occur and is probably related to nocturnal acidosis and dehydration.

Priapism

Prolonged sexual arousal, fever, cold exposure, REM sleep, full bladder, dehydration, alcohol, cocaine, and testosterone therapy have all been implicated as triggers

Splenic sequestration

One of the leading causes of death in children with sicklecell anemia is an acute splenic sequestration crisis.

Children with SS disease who have not yet undergone autosplenectomy.

Splenic sequestration

Patients suddenly become weak and dyspneic, with a rapidly distending abdomen,left-sided abdominal pain, vomiting, and shock.
Massive enlargement of the spleen with trapping of a considerable portion of the red cell mass.

Splenic sequestration

May be seen in association with fever or infection.

Splenomegaly due to pooling of large amounts of blood in the spleen.

Rapid onset of pallor and fatigue and abdominal pain is present.

Hb level may drop precipitously, followed by hypovolemic shock and death.

Hepatic sequestration

Sequestration can also take place in the liver. Tender hepatomegaly, increased anemia, reticulocytosis, and hyperbilirubinemia are the usual clinical features.

Because the liver is not as distensible as the spleen there is rarely pooling of red cells significant enough to cause cardiovascular collapse.

Diagnosis

A newborn with sickle cell anemia is not generally anemic and is asymptomatic because of the protective effect of HbF.
The "sickle prep" and solubility tests are unreliable during the first few months of life.

Diagnosis

Anemia and reticulocytosis are usually evident by ۴ months of age.
ISCs are frequently absent from the peripheral blood of young children, and the morphology is typical of that of normal newborns-target cells, fragments,and poikilocytes.

Diagnosis

By ٣ years of age, the typical peripheral blood smear is seen, including ISCs, target cells, spherocytes, fragments, biconcave discs, Howell-Jolly bodies, and nucleated red cells. The amount of HbF decreases with age, as in normal children, but it occurs much more slowly.

Laboratory findings

White blood cell count is often elevated.

Hemoglobin level often falls to below baseline values.

Thrombocytosis may be present and often follows an episode of ACS.

Secretory phospholipase ٢ (an inflammatory mediator) levels are elevated in ACS.

Other Hemoglobinopathy

Sickle cell trait

Sickle cell trait is a benign condition that is not associated with increased morbidity or mortality.
There is no associated anemia abnormal morphology, or decreased red cell survival.

Sickle cell trait

Electrophoresis in most individuals have approximately ٤٠% HbS and ٦٠% HbA.

Sickle cell trait

The most consistent abnormality found in sickle trait is an inability to concentrate urine. Persistent hematuria in sickle trait individuals has been associated with papillary necrosis of the kidney and rarely renal medullary carcinoma.

Sickle cell trait

Traumatic hyphema in sickle trait is a medical emergency because in the hypoxic conditions of the anterior chamber of the eye.

Sickle β- Thalassemia

Patients heterozygous for HbS and thalassemia have clinical severity that depends on the output of the thalassemic gene.

Sickle β- Thalassemia

Electrophoresis shows mostly HbS with slightly elevated HbA٢ and variable amounts of HbF.

Sickle β- Thalassemia(S β+)

One parent will have classic sickle trait, whereas the other will have thalassemia trait.

Sickle β- Thalassemia (S β+)

Electrophoresis in these patients shows predominantly HbS, elevated HbA٢,variable amounts of HbF, and HbA.

Sickle β- Thalassemia (S β+)

HbA,microcytosis, splenomegaly, and relatively benign clinical course.

The ameliorative effects of HbA.

Sickle β- Thalassemia (S β+)

These patients can be distinguished from individuals with sickle trait because of a higher percentage of HbS than HbA, microcytosis, hemolytic anemia, abnormal peripheral morphology, and splenomegaly

Sickle β- Thalassemia (S β⁰)

If no HbA is produced (S β⁰) the clinical course is comparable to that of homozygous sickle cell anemia.

Sickle β- Thalassemia (S β ·)

Electrophoresis shows mostly HbS with slightly elevated HbA٢ and variable amounts of HbF.

Sickle β- Thalassemia (S β ·)

Features that distinguish these patients from those with sickle cell anemia are that they may be of Mediterranean origin, have microcytosis, and often have splenomegaly.

Hemoglobin C

Homozygous HbC disease is a mild disorder characterized by hemolytic anemia, microcytosis, and splenomegaly.

Hemoglobin C

Anemia – usually mild, hemolytic.

Blood smear – numerous target cells, some spherocytes.

Hemoglobin electrophoresis – CC pattern.

Hemoglobin C

In HbC trait (Heterozygous Form, AC), target cell formation and mild microcytosis are the only manifestation of the anomaly.

Hemolytic anemia is not present(Asymptomatic)

Hemoglobin E

Heterozygotes (hemoglobin E trait) and homozygotes (hemglobin E disease) are asymptomatic

Hemoglobin E

The MCV is reduced and target cells are seen on peripheral blood smear.
Mild anemia is seen with hemoglobin E disease and less commonly with hemoglobin E trait.

Thanks For Attention