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Thalassemia

- Thalassemia refers to a group of genetic disorders of globin-chain production in which there is an imbalance between the α-globin & β-globin chai production.
- β^0-thalassemia: absence of β-globin chain production.
- β^+-thalassemia: ↓ β-globin chain production.
- β-thalassemia major: transfusion-dependent thalassemia.
- β-thalassemia intermedia: non-transfusion dependent thalassemia
- About 3% of the world's population carries alleles for β-thalassemia & 5-10% of Southeast Asia population carries alleles for α-thalassemia .
-There are > 200 mutations for β-thalassemia (most of them are rare, about 20 mutations represent 80% of the total).
- Normally, there are 2 β-globin genes & 4 α-globin genes, which → tetrameric globin protein which combines with heme → hemoglobin (Hb).

Pathophysiology

- Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as hemoglobinopathies. There are approximately 800 variant hemoglobin.
- After 8 wk of fetal life, the embryonic hemoglobins are formed: Gower-1 (ζ2ε2), Gower-2 (α2ε2), and Portland (ζ2γ2). At 9 wk of fetal life, the major hemoglobin (Hb) is Hb F (α2γ2). At approximately 1 mo of fetal life, Hb A (α2β2) appears, but does not become the dominant hemoglobin until after birth, when Hb F levels start to decline. A minor hemoglobin, Hb A2(α2δ2) appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 mo of age, and sometimes later. The normal hemoglobin pattern is >95% Hb A, ≤3.5 Hb A2, and <2.5% Hb F.
- In β-thalassemia, there are inadequate β-globin gene production leading to decreased level of normal Hb (HbA) & unbalanced α & β- globin chain production leading to ineffective erythropoiesis.
- In β-thalassemia, α-globin chains are in excess to non-α globin chains, which → α-globin tetramers (α4) which appear as RBC inclusions & free α-globin chains which are very unstable, precipitate in RBC precursors, damage the RBC membrane & ↓ RBC survival → anemia & ↑ erythroid production (massive bone marrow expansion) → lack of maturation of RBC & inappropriately low reticulocyte count. HbF (α2γ2) will increase & be the dominant Hb with increased HbA2 (α2δ2).
- In α-thalassemia, there is an excess of the β-globin & γ-globin chains relative to α-globin chains, which → Bart's Hb (γ4) in fetal life & HbH (β4) after birth. These abnormal tetramers are abnormal Hb with very high O2 affinity & → extravascular hemolysis.

- A fetus with more severe form of α- thalassemia (hydrops fetalis) develops in utero anemia & the pregnancy usually results in fetal loss because HbF production requires sufficient amounts of α-globin. In contrast, infants with β-thalassemia major become symptomatic only after birth when HbA predominates& insufficient β-globin production manifest in clinical symptoms.

Homozygous β-thalassemia (thalassemia major, cooly anemia)

Clinical presentations

- Patients usually become symptomatic during the 2nd 6 months of life (if untreated) due to progressive hemolytic anemia with profound weakness & cardiac decompensation (Hb is about 1-6 g/dl).
- Depending on the mutation & degree of HbF production, regular blood transfusions are necessary beginning in 2 months-2 years of life, but rarely later.
- The decision to transfuse is multifactorial including the degree of anemia & the presence of signs of ineffective erythropoiesis (such as growth failure, bone deformities 2ry to marrow expansion & hepatosplenomegaly).
- The classic presentation of children with the sever disease include thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, & catchexia & is primarily seen in countries without access to chronic transfusion therapy. Splenomegaly can develop with hypersplenism & abdominal symptoms. Pallor, hemosiderosis, & jaundice may → the greenish-brownish complexion of the patients color.
- The chronic anemia & increased erythroid drive → ↑ iron absorption & 2ry hemosiderosis-induced organ injury.
- Chronic transfusion therapy dramatically improve the quality of life & ↓ the complications of severe anemia, but transfusion-induced hemosiderosis become the major complication leading to high rate of hypothyroidism, hypogonadotrophic gonadism, growth hormone deficiency, hypoparathyrodism & DM. Iron deposition in the heart → heart failure & arrhythmia (the leading cause of death in inadequately chelated patients)

Laboratory findings

- In US, some children with β-thalassemia major will be identified on newborn screening as a result of detection of only HbF on Hb electrophoresis, but those with β^+ mutations might be missed if small amount of HbA are present.
- The lack of standardized neonatal diagnosis requires close follow-up of newborns with unclear thalassemia mutations & babies from high-risk ethnic groups.
- DNA diagnosis of β-thalassemia mutations, along with testing of common genetic modifiers of the clinical phenotypes is recommended.
- CBC & blood film: Hb level falls progressively often to <6 g/dL unless transfusion are given, microcytosis, hypochromia, target RBC, nucleated RBC, marked anisopoikilocytosis & relative reticulocytopenia are typically seen (the reticulocyte count is commonly <8% & inappropriately low to the degree of anemia due to ineffective erythropoiesis).
- Hb-electrophoresis: absence or ↓ HbA relative to HbF. Infants usually born only with HbF.

- The unconjugated serum bilirubin level is usually elevated, but other chemistries may be initially normal.
- Even without transfusion, iron eventually accumulates with ↑ serum ferritin & ↑ transferrin saturation.
- Bone marrow hyperplasia can be seen on radiographs.

Treatment

- Transfusion therapy: Patients should receive RBC depleted of leukocytes & matched for D, C, c, E, e & Kell antigens. CMV-safe units are indicated stem cell transplantation candidates. Transfusions should be given every 3-4 weeks, with the goal to maintain a pre-transfusion Hb level of 9.5-10.5g/dL. Monitoring for transfusion-associated infections (hepatitis A, B, C, HIV), alloimmunization & transfusion reactions is essential.

- Iron overload monitoring:

- Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels is useful in assessing iron balance trends but does not accurately predict quantitative iron stores.
- Quantitative measurement of liver (started after chronic transfusion therapy) & cardiac iron (started at 10 years old or earlier in sever iron overload) by MRI are standard noninvasive methods to measure tissue iron overload (estimation of pancreatic & gonadal iron is under study).

- Iron-chelation therapy:

- It should be started with significant iron-overload (generally after 1 year of transfusion therapy & with serum ferritin >1000 ng/mL &/or liver iron concentration of >5000 µg/g dry weight). There are 3 available iron chelators:

- Deferoxamine (Desferal): It has excellent safety & efficacy with poor adherence. It requires SC or IV route (short half-life of <30 minutes) as a continuous infusion over at least 8 hr daily, 5-7 days/wk (25 mg/kg-60 mg/kg). S/E: local skin reaction ototoxicity, retinal changes & bone dysplasia with truncal shortening.

- Deferasirox (Exjade, JadeNu): Oral route, half-life: >16 hr, given once daily (70% of patients have switched to it). 20-40 mg/kg/day (dispersible tab, Exjade) or 14-28mg/kg/day (film-coated tab & granule (JadeNu). S/E: mostly GI symptoms (↓ with film-coated tab), with potential kidney damage as the most serious S/E (↑ with dehydration) & occasionally hepatic transaminitis. All patients require monthly chemistry panels & monitoring for proteinuria.

- Defiriprone (Ferriprox): Approved in US as 2nd line, may be more effective to ↓ cardiac hemosideros, oral route, half-life: 3hr, 75-99 mg/kg/day, given 3 times daily. S/E: transient agranulocytosis (serious, 1% of patients usually in 1st year of therapy with rare deaths, requires frequen blood count monitoring (weekly for 1st year of therapy) & hold drug & check neutrophil count with febrile illness.

- Aggressive & combination chelation therapy is often used in heavily iron-overload patients to prevent or reverse organ dysfunction.

- Hydroxyurea: in some patients with β-thalassemia intermedia, associated with ↓ risk ofleg ulcers, pulmonary hypertension, & extramedullary hematopoiesis, 10-20 mg/kg/day, S/E: ↑ risk of cytopenia & requires monitoring of CBC.

- Hematopoietic stem cell transplantation: in low-risk HLA-matched patients (90% survival & 80% event-free survival), mostly in children <14 yr old without excessive iron stores &

hepatomegaly. Alternative transplantation without appropriate donor are experimental with variable success.

- Gene therapy: under study

- Splenoctomy: may be required in hypersplenism (falling steady state Hb level &/or ↑ transfusion requirements), less frequently used due to serious S/E beyond ↑ infection risk (in thalassemia intermedia → ↑ risk venous thrombosis, pulmonary hypertension, leg ulcers & silent cerebral infarction).

- All patients should be fully immunized against encapsulated bacteria & prophylactic penicillin should be administered after splenoctomy.

- Preventive monitoring of thalassemia patients:

1. Cardiac disease: Serial echocardiograms to evaluate cardiac function & pulmonary artery pressure (Pulmonary hypertension may occur in non-transfusion dependent thalassemia & may be an indication for transfusion therapy).

- Cardiac T2* MRI imaging study is recommended after 8 years of chronic transfusion. Intensive combination chelation therapy is required with decreased cardiac function. Periodic EEG after 10 year for arrhythmia.

2. Endocrine disease: Monitoring of endocrine dysfunction starts about 5 yr of age (or after at least 3 yr of chronic transfusion).

- Monitoring of height, weight & pubertal assessment semiannually. Bone density scan should be done on 2nd decade to detect osteopenia.

- Nutritional assessment are required (most patient need Vitamin D, C & zinc). Fertility should be assessed routinely.

3. Psychological support: Early social services consultation to address financial & social issues is mandatory

Other types of β-thalassemias

β-thalassemia intermedia:

- non-transfusion dependent thalassemia, but may be sporadically transfused, microcytic anemia (Hb: 6-10 g/dL).

- Complications depend on the degree of ineffective erythropoiesis (as medullary hyperplasia, HSM, pulmonary hypertension, leg ulcers, thrombotic events & growth failure), may require chelation therapy.

β-thalassemia trait:

- often misdiagnosed as IDA (IDA: more prevalent, response to iron therapy, ↑ RDW).

- There are microcytocis, mild anemia (Hb: 9-12 g/dL), normal RDW with Hb-electrophoresis(↑ HbA2 & variable ↑ HbF).

α-thalassemia

- It is most frequently found in south-east Asia.
- Infants are identified in the newborn period by ↑ production of Bart's Hb (γ4) during the fetal life & its presence at birth.
-There are 4 α-globin genes & 4 deletional thalassemia phenotypes as follows :

1. Deletion of 1 α-globin gene: silent carrier with normal appearance.

2. Deletion of 2 α-globin genes: α-thalassemia trait with mild microcytic anemia, can be mistaken as IDA, if both parents has the trait→↑ risk of hydrops fetalis, so family screening & genetic counseling are indicated.

3. Deletion of 3 α-globin genes: HbH disease with moderate microcytic anemia, splenomegaly, & jaundice.

- Treatment: monitoring of growth & organ dysfunction, dietary supplement with folate & multivitamins (especially vitamin D), splenoctomy is occasionally indicated, may need intermittent blood transfusion, may need chelation therapy & oxidant drugs should be avoided

4. Deletion of 4 α-globin genes: α-thalassemia major with hydrops fetalis, no normal Hb at birth, may need molecular diagnosis on fetal tissue, intrauterine transfusion may rescue the fetus, but congenital abnormalities & neurodevelopmental delay often result.

- If the patient is alive, he will be lifelong transfusion dependent & hematopoietic stem cell transplantation is the only cure.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PDD)

- This X-linked disease (mainly confined to males, about 140 mutations) affects more than 400 million people worldwide, representing an overall 4.9% global prevalence.
- G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains GSH (glutathione in the reduced, functional state). GSH provides protection against oxidant threats from certain drugs and infections that cause precipitation of Hb (Heinz bodies) or damage the RBC membrane.
- Most heterozygous females do not have evident clinical hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated (Lyon-Beutler hypothesis).

Variants

- The normal enzyme found in most populations is designated **G6PD B+**. A normal variant, designated **G6PD A+**, is common in Americans of African descent.
- Approximately 13% of male Americans of African descent have a mutant enzyme (**G6PD A−**) that results in a deficiency of RBC G6PD activity (5-15% of normal).

- Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian ethnic groups also have a high incidence (5% to 40%) of a variant designated **G6PD B−** (G6PD Mediterranean).
- A third mutant enzyme with markedly reduced activity (**G6PD Canton**) occurs in approximately 5% of the Chinese population.

Clinical presentations

- Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans.
- The most common manifestations of this disorder are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections (as hepatitis & sepsis), certain drugs, and fava beans.
- Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the hemoglobin concentration may fall precipitously.
- G6PD deficiency can produce hemolysis in the neonatal period. In G6PD A–, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B− and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. When a pregnant woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth. Neonate with co-inheritance of G6PD deficiency & Gilbert have more neonatal jaundice.
- Chronic non-spherocytic hemolytic anemia has been associated with profound deficiency of G6PD particularly with defective quantity, activity, or stability of the enzyme. Persons with G6PD B− enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.
- **Drugs** that elicit hemolysis in these individuals include aspirin, sulfonamides, nalidixic acid, chloramphenicol, nitrofurantoin, vitamin K analogs, methylene blue, and antimalarials, such as primaquine. The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency.
- In some individuals, ingestion of **fava beans** also produces an acute, severe hemolytic syndrome, known as *favism*. Fava beans contain divicine, isouramil, and convicine, which ultimately lead to production of hydrogen peroxide and other reactive oxygen products. Favism is thought to be more frequently associated with the G6PD B− variant (as in Iraq).

Investigations:

The onset of acute hemolysis usually results in a precipitous fall in Hb and hematocrit. If the episode is severe, the hemoglobin binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine.
- Unstained or supravital preparations of RBCs reveal precipitated hemoglobin (**Heinz bodies**) which are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood.
- Also, the blood film may contain red cells with what appears to be a bite taken from their periphery (**bite cells**) and polychromasia (evidence of bluish, larger RBCs), representing reticulocytosis.

- The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal .This reduction

is more extreme in Americans of European descent & Asian than Americans of African descent.

- Screening tests are based on reduction of methylene blue, reduction of methemoglobin or fluorescence of NADPH.
- Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A− variety (Africans), so testing should be deferred for a few weeks before a diagnostically low level of enzyme can be shown.
- The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by electrophoretic and molecular analysis.

Prevention & treatment

- Prevention of hemolysis is the most important therapeutic measure. When possible, high risk ethnic groups should be tested for the defect before known oxidant drugs are given & in sever neonatal jaundice.
- If severe hemolysis has occurred, supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.